SURGERY

VOL. 8 AUGUST, 1940 NO. 2

Mayo Memorial Volume

A miscellany of papers written in honor of two distinguished American surgeons

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EDITORIAL PREFATORY NOTE

THE name, Mayo, has been engraved indelibly in the annals of surgery by the achievements of the brothers, William James and Charles Horace Mayo. Their own accomplishments and what they did for surgery will keep the name of Mayo unfaded in the memory of men when these printed words have grown dim with the desolation of time.

During their lifetime, the brothers Mayo declined modestly the suggestion of a memorial volume, acknowledging with a genuine expression of gratitude, however, this mark of esteem and affection of their friends.

These pages are written by admiring colleagues to do honor in death to the memory of two illustrious surgeons and distinguished Americans who lightened the burdens and brightened the lives of thousands of families. The influence of the work of these men has been felt wherever medicine is practiced, whether in the largest cities or the most remote places throughout the world. Their lives should be helpful and stimulating examples for surgeons everywhere.

WILLIAM JAMES MAYO (1861-1939) AND CHARLES HORACE MAYO (1865-1939)

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IT WAS during the remarkable half century in the history of medicine from 1880 to 1930 that Dr. William J. Mayo and Dr. Charles H. Mayo lived their active professional careers, for they began the practice of medicine with their father, Dr. William Worrall Mayo, in the 1880's and continued their practice until their deaths in 1939.

In 1855 the father settled in southern Minnesota and began the varied practice of a pioneer physician and surgeon. His two sons in their early youth, while still in public school, often accompanied their father on his professional rounds and assisted him in those emergencies which largely comprised a general practice of that day, and in their summer vacations they gained a practical knowledge of pharmacy by working in a drugstore. There never was uncertainty as to their studying medicine. In later years Dr. W. J. Mayo wrote: "To grow up in a doctor's family with a professional background of some generations will likely have, as it did with my brother and myself, that sort of influence which leads, not to conscious choice of medicine as a career, but rather to unconscious elimination of every other choice. Neither my brother nor I ever had an idea of being anything but a doctor."

The incentive which led both brothers to train themselves for a surgical career may be found in their early experiences and in their father's interest in surgery, for in 1871 William Worrall Mayo reported the successful performance of an ovariotomy, and in the next thirteen years he carried out thirty-six similar procedures. There is also to be remembered the fact that William J. Mayo and Charles H. Mayo entered practice at about the period when the great advances of modern surgery were initiated.

The problem of acquiring a knowledge of surgery and keeping abreast of its advances was a difficult one to solve for these busy country practitioners in a small town. One essential in its solution was travel, and they were indefatigable, thorough, and persistent in this means of education. They early agreed that 25 per cent of their gross income from their practice should be set aside for education and research, and since their environment could not afford them adequate opportunities, they traveled in this country and abroad to observe the work of those who were more fortunately situated in regard to facilities, training, and clinical material. Their travels were on an exactly ordered plan, for they sought and saw only things that were done better than they could do them. One of the brothers always was at

home, the only notable exception being a visit which they made together to England in July, 1929, to be present at the dedication of a window they had given to the little parish church at Eccles, near Manchester, which their father had attended as a boy. In each clinical journey they had a specific purpose of learning some new surgical procedure by actual observation of its performance and of becoming acquainted with the leading surgeons of the world and their approach to the rapidly developing field of surgery.

From the beginning of their careers to the end, the brothers carried out in Saint Mary's Hospital both the application of the knowledge acquired in their travels and the contributions which they themselves made to surgical progress. At its opening, in 1889, Saint Mary's had twenty-five beds. From its beginning, this hospital received all classes of patients without regard to creed, color, or financial or social condition. A small band of the Sisters of Saint Francis was the administrative and nursing staff, and with few and untrained helpers these devoted women carried on the work. The confidence of the Sisters in Dr. William Worrall Mayo, for it was he who had supported them in the building of the hospital, was extended to the sons, and a perfect mutual understanding and trust continued throughout their lives.

This original group of physicians and nursing staff never lost the simplicity of method which was characteristic of the surgery of that time. In their surgical work the Drs. Mayo had the aid of Sister Mary Joseph, who died in the same year as the two brothers and of whom Dr. William J. Mayo wrote:

"In this early group Sister Mary Joseph, by reason of character, energy, and intellectual ability, took a prominent place. She became matron and director of the hospital, which position she held until her death. Executives of the caliber of Sister Mary Joseph are born, not made.

"Sister Joseph promptly mastered, to an extraordinary degree, surgical technique and procedures from the standpoint of the surgical assistant, a position in which she served for twenty-five years, working directly across the operating table from me. Possessing great keenness of perception, unusual clinical acumen, and an extremely delicate sense of touch, she aided me during the operations, performing technical maneuvers with rare facility. Her surgical judgment as to the condition of the patient, before, during, and after operations was equal to that of any medical man of whom I have knowledge. Of all the splendid surgical assistants I have had, she easily ranked first."

The unique relationship which existed between the Drs. Mayo and such a surgical assistant, who also was matron in the hospital, contributed in no small measure to the results of operations which the Drs. Mayo were able to report in their early years of surgical practice.

Throughout the following years, the surgical work of the Drs. Mayo continued, and the results of their experience are recorded in the variety and character of their publications. Their writings stand as evidence of their numerous original contributions in many fields and of their recognition of the contributions of other surgeons and scientists. Their publications also are proof of their realization that to bring about advance in any field of surgery intense specialization based on adequate experience and knowledge of general surgery is necessary. In their early practice William J. Mayo and Charles H. Mayo were required to engage in every department of surgery, and it was only when they secured associates who were especially trained in many of these branches that they found it possible to restrict their own work to the surgical fields with which their names will always be associated.

The influence which these two men had on surgery and surgeons, on their associates, and on those whom they trained, came from the consistency with which they searched for the truth. From their earliest days of practice, the brothers, taught by their father, realized that the chief cause of error in diagnosis is incomplete examination, and in teaching and practice they stressed every means of acquiring as complete knowledge as possible of every patient. The early clinical records of both father and sons are models of careful observation and direct deduction. Their determination to know the truth led them to secure necropsies whenever possible and, as a result of their teaching, the division of pathologic anatomy in the institution they founded at present is granted permission for necropsies in over 80 per cent of deaths.

William J. Mayo emphasized always the desirability of utmost use of the physician's native intelligence in dispelling what he called "diagnostic fog"; by this he meant the confusing of the issue by too great reliance on laboratory and mechanical aids to diagnosis, invaluable though they are. In his homely and classic article, "In My Father's Time," he began by writing: "Clinical diagnosis in my father's time was based to a large extent on examination by the five senses aided by a few instruments of precision." The fact that the brothers were not eager to adopt the many new accessories which rapidly were offered for use in medicine and surgery may have had much to do with the development of their resourcefulness, their extraordinary clinical judgment and skill in diagnosis, and their adaptability to every sort of surgical situation. And throughout the years, in the building and development of their great adventure in group practice and medical education, while William J. Mayo and his brother and their associates encouraged every advance in medical research and employed every scientific aid, their sound common sense and wise discrimination were always evident.

In the early days the routine work of the office practice and the hospital required the personal care of the father and his two sons, and their unremitting feeling of mutual responsibility became a habit which carried through their entire lives. Always, when one of the brothers

was away, the other saw personally the patients on the services of both. Day by day, year after year, they observed an unvarying operating room ritual. For many years the brothers both operated every day, and their routine was much the same; that is, they began hospital rounds shortly after seven o'clock in the morning and operations promptly at eight o'clock.

As surgeons, William J. Mayo and Charles H. Mayo were distinguished by an amazing ability to focus on essentials and by good judgment based on enormous clinical experience. They were excellent technicians, carefully but not unnecessarily attentive to detail. While the two men differed in approach and technique, the work of each was marked by confidence, a high sense of responsibility, quick and steadfast decision and directness of attack. They were scrupulous in avoiding operation unless they believed the patient would be greatly helped, but they always offered the patient the benefit of operation if any doubt existed, particularly in the presence of malignant disease.

In all their years of intense activity in surgical practice they found time for daily reading and clinics. Dr. William J. Mayo for many years followed a routine of lying down between operations, and in these periods of physical relaxation he did much of his medical reading. He urged systematic medical study for surgeons and said: "I began by charging myself with one hour's study a day, and I did not give myself credit for advance work; that is, if I put in three hours, I took credit for one. I was scrupulous, however, in making up the deficit when it happened that I was unable to study. It is surprising how much one can accomplish by adherence to this type of program. The reading should be catholic. To the young surgeon I would say, do not read all surgery and technique, for technique is constantly changing. We abandon procedures which were perfectly satisfactory, for something which is no more satisfactory, as the ladies do their bonnets. Along with surgical literature, read medical articles in high class medical journals. Do not skim, but here and there select certain articles and read them with care, especially those that have a physiological background.

"Further, I would advise the young surgeon to write papers, and in writing to bear in mind what the old minister said, 'Few souls are saved after the first fifteen minutes of the sermon.' Write the paper not to show how learned you are, or to show the high type man who may be in the audience, that you are in his class. Rather, try to tell those in your audience, who perhaps may not know as much about the subject as you do, something that may interest and help them. Do not try to make too many points. . . . . "

Throughout their careers these men carried on with their colleagues, a weekly conference for review of their own work and that of the profession in all parts of the world as represented in the literature and

by the travels of themselves and other members of the staff. I well recall that more than thirty years ago these meetings were held in alternate weeks in their two homes, and I remember the impression made on younger associates of the purpose of such conferences, to know the truth regardless of how unpleasant it might be.

Tolerant and understanding in all relationships, these brothers were exponents of freedom of speech and thought for their associates and themselves. In no way did they ever seek to interfere with religious, political, or social opinions, and they made this attitude a tenet of belief for the institution as a whole.

The Drs. Mayo were conscientious and enthusiastic in their attendance at the meetings of medical societies: county, state, district and national, special, and international. They believed and taught that a physician's standing in the medical profession depends on the manner in which he realizes his duty to medical organizations; that is, it is only as "we have respect for and are willing to make some sacrifice for our home organizations that the public will recognize and value the medical profession."

In their papers, addresses, and teachings they endeavored to present professional matters in such way as to be entirely impersonal, and discussed only such questions as they believed would be of benefit to the profession which they loved and in which they lived all their lives. They held to the tenets of the American Medical Association, for they believed that, since this organization represents the profession of America, it should have the support of members of the profession. They were attentive to the recent trends, believing that the attitude of the profession toward socialization of medicine is one of sincere desire for information, to learn in what way their activities can be adjusted to inevitable social changes as they come, only hoping that the quality of medical care which the profession is capable of rendering today will not be lessened.

As teachers William J. Mayo and Charles H. Mayo early recognized that an adequate training in general diagnosis and a firm groundwork of instruction in fundamental fields were essential to sound surgical practice. In the operating room they were actuated by a genuine desire to give opportunity for development to their assistants, to permit them to participate in the operations sufficiently not only to become familiar with the principles of surgery, but to acquire adequate technical skill.

The purpose and manner of their teaching in the early years culminated in the Mayo Foundation for Medical Education and Research. The training provided by the Foundation in the last twenty-five years has been based on the general plan followed by Dr. William J. Mayo and Dr. Charles H. Mayo for the many years preceding the establishment of the Foundation and its affiliation with the University of Minnesota. They gathered assistants about them, not primarily to secure aid in surgery and clinical medicine, but because they had a real de-

sire to teach, with tolerance, patience, and consideration, with careful guidance, for the advancement and spread of knowledge, toward the better care of the sick and the strengthening of the profession. Their experiment in graduate medical education has established the soundness of the principles upon which they based their work and their teaching, for their methods have been continued on a university basis without radical change.

To have practiced medicine with distinction for fifty years and more, and to have won the respect and affection of colleagues and confreres, is a high achievement. William James Mayo and Charles Horace Mayo did not seek honors and rewards. The distinguished recognition which came to them they accepted with gratitude, untouched by pride and self-esteem, because they believed that it was bestowed not on them alone but also on those who had served with them in the work they loved.

A PERSONAL APPRECIATION OF THE MAYOS AND THEIR WORK

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I HAVE been asked by the editors of Surgery to prepare something personally reminiscent of the Mayo brothers and the splendid work done by them. This is indeed a difficult, though pleasant, task that has been set me, not only because of the extraordinarily attractive personalities presented by these two devoted brothers, but also because of the unusual character and wide extent of the work accomplished by them in their busy lives. It will be impossible in the short space allotted me to give anything like an exhaustive account of what they and their associates in the Mayo Clinic have accomplished, or what it has meant to the medical and surgical professions at large. I shall not attempt, therefore, to do more than refer to a few of the more outstanding contributions as I see them that have come out of the Clinic, and to appraise as best I may the effect that this unique institution, during its more than one-half century of activity under the guidance of these two extraordinary brothers, has had upon the progress of medicine and surgery.

In the recent death of the Mayo brothers, William James Mayo and Charles Horace Mayo, the world of surgery has suffered a grievous loss. In their work they were always so closely associated with each other in the minds of their friends and associates of the profession that it is impossible to think of one without the other. The example which they have set in devoting their lives to the betterment of their profession is certainly one for succeeding generations to emulate. Not only did they witness in their lifetime the phenomenal development and growth of modern surgery, but they themselves contributed to it in large measure.

Aided and stimulated by their remarkable father, William Worrall Mayo, they brought about a new development in the practice of medicine and surgery; namely, the gathering together of a group of men well trained in the different departments of medicine, and the establishment with their aid of a Clinic for the twofold purpose of studying and treating diseases of all kinds and of training physicians and surgeons along scientific and practical lines. Their Clinic, a model of its kind, has contributed greatly to the science and art of surgery. The Mayos have shown what can be accomplished by means of thorough organization, careful selection of capable and well-trained personnel, and unfailing perseverance in the pursuit of an ideal. Anyone who has visited Rochester, Minn., and has familiarized himself at all with the character and extent of the work done there must have been deeply impressed by what has been accomplished.

As I write, my mind goes back to the early days of a half-century and more ago, when the Clinic had its origin largely as the result of the cyclone of 1883 which passed over the town of Rochester, Minn. The history of the subsequent progress and development of the Clinic strongly reflects the rugged character of the early settlers, who, as a result of their training in the school of experience, were accustomed to meet and overcome the difficulties inherent in the primitive life of the great West.

In reviewing the work that the Clinic has done, it is extremely difficult to evaluate at their true worth the various elements that have contributed to make it what it is. The idea of establishing such a clinic seems to have originated in the fertile brain of the senior Dr. Mayo, but it was taken up very early by Dr. Will, ably seconded later by Dr. Charlie. It wasn't long thereafter before the name of Mayo began to be on the lips of surgeons everywhere and to appear prominently in medical journals and on the programs of surgical societies all over the country. The attractive personal characteristics of the Mayo brothers made them exceptionally welcome in any surgical gathering. The authoritative character of their scientific papers and discussions was such as to command general attention. Before long the eyes of the surgical world were turned toward Rochester, and in course of time it became the surgical Mecca of this country.

I can recall with great satisfaction my first visit to the Mayo Clinic in the early nineties. The character and amount of work done here in this prairie town were most impressive. The two brothers were, each in his own way, most interesting characters, and their devotion to each other was a pleasure to see.

As is usually the case, after starting out in the traditional way of doing everything that offered, they early began to specialize more or less in their work. Dr. Will devoted the most of his time and attention to the abdominal organs, while Dr. Charlie was a sort of all-around specialist, however, perhaps devoting most of his attention to the treatment of the various types of surgical diseases of the thyroid gland. The wealth of material furnished by the Clinic along these, indeed along all, lines enabled the Mayos to speak with the authority of wide experience upon many subjects. One had but to visit the Clinic and study it in operation to see the crowds of patients who regularly flocked to its doors; to spend a few days in the operating rooms and wards, to attend the various conferences and demonstrations of pathologic specimens, to be impressed with the value and extent of the work done by it and the power for good along all lines of professional endeavor that it was capable of exerting, and did exert, upon the profession at large. No wonder then that under the skillful guidance of the Mayo brothers there was developed out on the prairies a medical center which became the wonder of the civilized world.

As additional evidence of the type of men the Mayos were, they were not spoiled by their success or the many honors heaped upon them by institutions of learning both in this country and abroad. They remained to the end always the same charming, approachable, human men, a delightful stimulus to their professional friends, a tower of strength to their patients, and benefactors to mankind.

While it may be true, as claimed by some, that their individual contributions to scientific surgery were not outstanding, still it is an open question as to which confers the greater benefit upon mankind, the simple discovery of a scientific fact or the practical application of that fact to human needs and the popularization of it so that the greatest good therefrom will come to the greatest number. Although it is undoubtedly true that sufficient time has not as yet elapsed to afford a true perspective as to the lasting effect upon the practice of surgery of the contributions of the Mayo brothers, time and accumulated experience will determine the true verdict. Meanwhile, informed members of the medical profession, surgeons in particular, are confident that the progress of surgery as a whole has been tremendously advanced by the judicious testing of the newer methods and by the mature judgment of the Mayo brothers.

For many years the Mayo Clinic has furnished, as it were, a Supreme Court for estimating the real value of the various new surgical procedures suggested from time to time. What a satisfaction to a young, inexperienced surgeon to know that a certain surgical procedure has the approval of the Mayos! With how much greater confidence and assurance he attacks his problem! Along the special lines indicated above, the brothers have each made substantial contributions to our knowledge of the subjects treated. The mistaken idea that seems to prevail in certain quarters that surgical research is confined to operating upon animals has been largely disproved by what has been accomplished in the Mayo Clinic. The additions to our knowledge as to the causation, clinical history, the simplification and perfection of the operative technique in the treatment of the surgical affections of the gastrointestinal tract and the thyroid gland, to mention only two subjects, are such as to establish beyond question the research value of the work done by them. The impression that has been made upon the practice of medicine and surgery by the Mayo brothers through the Clinic established by them has been far reaching, and its beneficent effect will be lasting for generations to come.

THE MAYOS AND THEIR WORK

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DR. WILLIAM J. MAYO and Dr. Charles H. Mayo came of a line of physicians which had extended back to the middle of the seventeenth century. Their father, Dr. W. W. Mayo, was an outstanding physician and surgeon who had been instructor in chemistry and physics at the Bellevue Hospital Medical School before receiving his medical degree from the University of Missouri. During the Civil War he was provost surgeon for Southern Minnesota and in charge of recruiting stations. In 1863 he moved to Rochester, Minn., which was to become a world mecca. With the indefatigable and progressive spirit manifested later by his distinguished sons, Dr. W. W. Mayo took a postgraduate course in medicine and became a leader and organizer of local and national medical societies. He was also the founder of St. Mary's Hospital which has played so prominent a role in the development of the Mayo Clinic.

William J. Mayo graduated in 1883 from the University of Michigan Medical School and his brother, Charles H. Mayo, graduated in 1888 from the Medical School of Northwestern University in Chicago. As the inclination of each was toward surgery, they began their surgical experience under their father's guidance at St. Mary's Hospital in Rochester.

From the very beginning the active personality of Dr. W. W. Mayo had appreciated the advantage of the association of the practicing physician with the practicing surgeon. His feeling as to the importance of this conception in general diagnosis was emphasized by his association with the practicing surgeons of his time. Thus, the "group" idea really originated with Dr. W. W. Mayo.

To me, as I knew Dr. W. W. Mayo in his later years, his spirit was well illustrated by the fact that in his eighties he took a trip to Japan alone, "to keep from getting rusty," as he put it. It is my impression that had he started where Will and Charlie began he would have had a similar brilliant career—considering his originality, vitality and his appreciation of group practice.

Dr. W. W. Mayo's two sons as students assisted him with his patients and with minor operations. He chose for them two excellent medical schools; after their graduation they began to practice with him, so that no small part of their clinical training and of their impressions of the value of group practice they derived from their father's practice.

It will be of interest to compare the state of the science and the art of medicine in 1883, when the elder of the two brothers began his practice, with the general status of the United States then. At that time the total population of the United States was in round numbers, 50,155,000; Chicago had a population of 503,000; New York City, a

population of 1,911,000; and Cleveland, a population of 160,000. At the present time the population figures have jumped to 129,257,000 for the United States; 4,364,000 for greater Chicago; 7,960,000 for greater New York, and 1,271,000 for greater Cleveland. With this growth in urban population the Mayo Clinic with its rural setting kept pace.

Thus the vigorous seedling of group practice planted by Dr. W. W. Mayo was fostered and nursed by his two famous sons, not only under the most rapid development and expansion of the United States through the tide of immigration which has continued to rise until the present time, but also under the most rapid development in the science and in the art of medicine.

It should be remembered that, when Dr. W. J. Mayo graduated from medical school in 1883, anesthesia was in its infancy, for, although anesthetics had been administered since 1846, the favorable and unfavorable indications for the depth of anesthesia under varying conditions were but little understood.

Only sixteen years before Lord Lister had published his revolutionizing treatise, *On the Antiseptic Principle in the Practice of Surgery,* which converted the operating rooms of that time from pestilential chambers to the aseptic perfection they now represent. At that time a carbolic spray was used freely in the operating room, and septicemia and wound infections were such a menace that the skull, abdomen, bladder, joints, bones, and spinal cord could not safely be operated upon. To be sure the abdomen was opened and a limited range of operations was performed, but infection often proved fatal. Surgery then was largely devoted to the care of accident and emergency cases; at that time there were almost no cases of cured carcinoma of the breast or uterus.

The entire medical practice in the 1880's was sharply divided into either general medicine or general surgery, with none of our present-day specialization. The general medical man took care of pediatrics, obstetrics, and psychiatry, while the general surgeon corrected deformities, set bones, operated upon the urinary tract, removed tonsils and adenoids, and removed injured eyes. The Mayo brothers were such general surgeons, their practice consisting of attending whoever was sick whether the problem was surgical or not.

In the 1880's and 1890's there was no neurosurgery and no genito-urinary surgery; all the specialties were taken over by the general surgeon. So, Dr. W. J. Mayo and Dr. Charles H. Mayo in common with McBurney and Bull (New York), Richardson (Boston), Keene and Gross (Philadelphia), Halsted and Finney (Baltimore), Murphy and Ochsner (Chicago), Huntington (San Francisco), and Matas (New Orleans)—in common with all of the men of this period, they enjoyed the thrill of excitement in the opening of the various fields: the surgery of the abdomen, the removal of pus tubes, the various opera-

tions for carcinoma, the opening of the skull for tumor, the removal of diseased kidneys. A little later the Mayo brothers took part in the opening of the field of goiter and neck surgery, the field of surgery for peptic ulcer, and the extension of plastic surgery. They also had the adventure of seeing the development and extended application of local and general anesthesia, blood transfusions, the prevention of shock, and the better preparation of patients to withstand surgical operations.

Dr. W. W. Mayo died in 1911 happy in the knowledge that during his lifetime the groundwork laid by Pasteur and Lister had permitted the development of brain surgery and cancer operations to such a point of safety that these difficult procedures could be undertaken with the same amount of ease as a hernia operation was handled during the days of his earlier practice.

It had been the good fortune of the Mayo brothers to travel widely in America and abroad and thus to bring back new ideas to their Clinic. They early applied the principle initiated by their father of associating themselves with men skilled in diagnostic methods. They, and the other men who shared this period, had the privilege of rising with the tide of immigration and increasing wealth, together with the upward spiral of advancing medical discoveries. And with this they were able to see the extension of the principle of group practice in many parts of the United States and especially in the development of their own Clinic in Rochester, Minn.

In view of the fact that agriculture and industry have reached a more stable condition and in view of the fact that their progression has not quite so much room for expansion compared with the enormous advances made since 1883, it is not probable that an advancement equal to that of the last fifty years can be expected in the coming fifty years as far as surgery is concerned. The great advances will be in internal medicine and in a better understanding of the physical nature of the animal mechanism through physics and chemistry. With this better understanding of the physical nature of the animal mechanism will come a great expansion in the field of preventive medicine.

The Mayo Clinic Foundation in the past has been a leader in the application of each new advancement in the entire domain of medicine, surgery and its specialties. The Mayo brothers have generously contributed in research to the art and the science of medicine in their period of activity and have set up an endowment fund to perpetuate their work. During their lifetime they contributed to the sick man of today, and in their perfectly organized Medical Clinic they are contributing aid to the sick man of tomorrow. This constitutes a great memorial, not only to Dr. William J. Mayo and Dr. Charles H. Mayo but also to their father, Dr. W. W. Mayo.

PUBLIC OPINION AND ANIMAL EXPERIMENTATION

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> What is it to have lands and houses, to abound in silver and gold, to be decked with pearls and diamonds, yes, and to possess the whole world, to rule Nations and countries, and to lack health, the chiefest jewel and greatest treasure of man's life and delight.
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> —*Thomas Vicary*, 1548.

THERE could be no more appropriate place for a discussion of animal experimentation than in a collection of papers dedicated to the brothers, William and Charles Mayo. Their good deeds for suffering humanity, every fragment of their life's work, and the very pedestal on which their success depended were derived from animal investigation. It is time that every doctor took up the cudgels in defense of experimental medicine and explained to the laity how the advances in the healing art have come about largely through the use of animals. In particular, it should be understood that the science of bacteriology is the very basis of surgical practice. Before the advent of bacteriology, surgical operations were attended with almost inevitable sepsis, so that hospitals came to be looked upon by suffering human beings as places definitely unhealthful for them to enter. With the coming of the study of bacteria as the cause of infection and with slow and continuous animal investigation, which proved not only how bacteria cause disease in living matter but how the bacteria can be killed off so that infection is not passed from individual to individual, came the first steps in modern surgical advance. On these animal investigations are securely erected our present methods of sterilization. Without such methods, the surgery of today could not exist. It would appear that these facts are not widely disseminated among the public.

The extraordinary interest of the news-reading public of today in scientific matters is an excellent gauge of the spread of education to all classes of our people. This general inquisitiveness for scientific knowledge has led to a special interest in those matters dealing with public health and, indeed, with all medical affairs. Man, having spent centuries discussing his soul, has at last become interested in his body.

There appears to be some justification for this special interest in modern medicine, for (1) the great extension of life in recent years, due largely to man's knowledge of the role of bacteria in infectious diseases and hence of how to avoid infections; (2) the recent successful attacks on other types of disease, as seen in the present methods of treatment for diabetes and pernicious anemia; (3) the rapid progress of surgical therapy to the point where a majority of our citizens have at some time

benefited from this form of treatment; and (4) the recent experiments emphasizing the tremendous roles that minute quantities of chemical substances, known as hormones or vitamins, may play in life—all give evidence that modern medicine is indeed one of the most brilliant movements in applied science.

Whether this public interest is something deeper than curiosity and whether it can be relied upon as a potent factor for the common good have not been demonstrated. Indeed, a study of the historical background of surgery invokes in the mind of the medical scientist a distrust of the public. One has only to recall the many great figures of science who were either scorned by the people or actually tortured, because their discoveries, soon to benefit mankind, seemed at the time unorthodox. It may not be common knowledge that Michael Servetus, who discovered the pulmonary circulation, was burned at the stake along with all his books because he dared to state the truth. And we have only to mention that during the Middle Ages the Church frowned upon anatomy and surgery, and that the Edict of Tours (1165, *Ecclesia abhorret a sanguine*) declared surgery was not respectable. The feeling became so strong that the School of Medicine at Montpelier issued a decree that none of the students should practice or study surgery.

Even recent American medical history is replete with incidents of how the public attitude erected barriers to progress. It should be common knowledge that Dr. Zabdiel Boylston, of Brookline, Mass., when he first inoculated a man for smallpox, was chased by a mob, and that his life was threatened so that he had to hide in his house. The early history of the Harvard Medical School is a good example of the dangers involved in teaching medicine. Obviously, anatomy had to be taught, if the public were to receive the benefits of good medical practices; yet bodies were not procurable. Grave robbing was resorted to, causing difficulties with the police which have been vividly described by J. C. Warren,[1] later to become Professor of Surgery and Anatomy. His experiences emphasize how greatly public opinion is influenced by sentiment, not reason, and how such a sentimental view may impede progress.

Less than a century ago there was no anesthesia in the modern sense; bacteria, as the cause of infectious diseases, were unknown; and medicine, as we know it today, did not exist. In 1846 ether was discovered and given to the world (chloroform appeared the next year). Then the "dark days of medicine" ended, only to return to confound and terrorize both physician and patient as operations were followed by infection. To be sure, men could be put to sleep, and the terrible disorders from which they suffered could be removed painlessly with the knife or the cautery. But this gift of anesthesia proved at first a curse, for man did not understand at this time that bacteria lurked everywhere. The doctor did not know that his instruments carried filthy organisms, and therefore death, to his patient. The slightest use of the scalpel

meant grave infection. Women put to sleep to ease their pains during childbirth were infected by the doctors who sought to bring them comfort. No wonder that in those times people looked askance at hospitals and feared to go to them!

It was a full thirty years more before the discovery of bacteria by Pasteur and Koch and the application of their discovery to surgery by Lister taught the medical profession that, if they would make progress, they must study bacteria; they must find out how bacteria give rise to diseases; and they must learn how to rid the operating rooms and the hospitals, as a whole, of bacteria. The innumerable experiments upon animals necessitated by these studies undoubtedly resulted in suffering for a great many creatures. We should not hide the fact, but now we, who benefit from these studies, should make acknowledgment both to the animals, who have made our lives safer and more comfortable, and to the investigators, who had the courage in the face of hostile and bitter criticism to carry forward their works. We should not have known how to sterilize all the materials used in operating rooms today, unless we had found out upon animals what organisms did when they entered a living body. Thus, every person today whose life has been saved or made more comfortable through a surgical operation owes a deep debt of gratitude to the animals concerned with this development. One should not deceive people. Though there be those who object perhaps to what has gone before, they must be willing to balance against these experiments on animals the thousands of children saved from diphtheria and the countless lives made comfortable through surgical operations for acute appendicitis, strangulated intestines, or tumors of the womb.

Not only has man benefited from these experiments, but the animals themselves have benefited. Texas fever, which at one time destroyed a great part of the cattle bound for the meat markets, has now disappeared because Theobold Smith used a few animals in studying the transmission of the disease from steer to steer through a tick. Similarly, hog cholera, which decimated swine, is now under control because of a few animal investigations. The foot and mouth disease, through a similar group of experiments, has practically disappeared from this country. Indeed, experiments made to protect animals have frequently resulted in benefit to man. Thus, the drug which Maurice Hall found would cure hookworm disease in dogs later proved effective in man and alleviated the suffering of millions of our own genus in the South. And what of the beneficial and helpful surgery now performed on horses, cows, and dogs for their own good and comfort? The great good to animals that goes on in the many splendid animal hospitals set up by Humane Societies could not exist unless the role of bacteria in relation to infection had been discovered by animal experiments. Think of the protection to animals given by vaccination for rabies, for horse encephalitis, and for distemper!

This brief recital of the advance of medical progress is but a promise of the future. Do our people know why, in the graveyards of New England, so many wives lie beside one husband? Do the rows of little stones about the headstone of a family mean nothing? The history of bacteriology is available to all. Can they envisage their great-great-grandfathers strapped to a wooden table and writhing in pain whilst the best surgeon of that day groped in his dirty bag for the knife with which he opened the bladder for removal of a stone that made life a hell on earth? The blessing of anesthesia has done away with all this suffering. Why is it that so much smugness settles upon a comfortable people? Our citizens avoid these terrible calamities because scientists have toiled in the night against the same complacency that now encompasses this generation. Our ancestors made laws that made the proper study of disease a crime. Bodies were not allowed for dissection, and the use of animals was decried. A few saw the light of greater comfort and happiness, and struggled on, criticized by the "good people" of their day, chased by the police, and blasphemed by those they sought to help. These few had to rob graves of their occupants in order to teach the next generation enough anatomy to bring comfort to our generation. Experiments upon animals were surreptitious affairs.

The laity will smile at this recital of earlier days, but are they really helping their own generation and the generations to follow in any better fashion? Do they know where the bodies needed to educate those who are to care for their children come from? Each year the number available decreases. The coroner takes the bodies of the criminals and every accidental death, even if he does not examine them. The State Hospital official is afraid of criticism if he gives up bodies, even under the law. In at least one state a law has even been proposed that the state give proper burial to unclaimed people, a move which would destroy even the meager supply now remaining. Soon the young doctor will have to learn his anatomy on living bodies, i.e. his patients! And as for animals—over 50,000 are sacrificed each year by a single Animal Rescue League, while the scientists must pay great prices for strays brought to them. One can properly state that about $1,000,000 is paid out each year for animals used in research laboratories in the U.S.A., while a hundred times more animals than would be required are put to death by Animal Rescue Leagues, etc. Thus, $1,000,000 a year which might be devoted to the care of human suffering is needlessly expended.

How does this come about? Because the healthy citizen neglects his duty of citizenship and allows a misguided minority to inject sentiment into our laws, to set aside reason, and thus to jeopardize his health and the health of his family. Each year new laws are proposed making the use of animals for scientific purposes more difficult. Each year workers in laboratories must stop work and hie themselves to Committee Rooms in the State Houses of our country, there to be maligned as cruel mon-

sters, in order to defend the present laws and to prevent the passage of new laws that would make fruitless the continuance of their efforts for the relief of suffering. The people who attempt such changes in laws often wear feathers, plucked in some instances from living birds; they eat meat which is more tender because a farmer without an anesthetic removed a part of the animal's body with a knife, when the animal was young; they often wear around their necks furs secured from animals trapped in the north and allowed to freeze to death with a leg broken in a steel trap. Fur trappers have stated that, for every fur brought in from traps, two to five other animals have been eaten from the trap by predatory birds and beasts. And they call scientists cruel! All the laboratory experiments of the last fifty years have not caused as much suffering as the preparation of meat for our markets in a single year!

The use of animals in laboratories is carefully protected. The following rules hang in each reputable laboratory in the United States and are carefully enforced. These rules are based on the principle that animals in laboratories shall be afforded the same care that is given patients in hospitals and that the infliction of pain shall be avoided in the same manner as it is in hospitals.

RULES REGARDING ANIMALS

I. Vagrant dogs and cats brought to this Laboratory and purchased here shall be held at least as long as at the City Pound, and shall be returned to their owners, if claimed and identified.

II. Animals in the Laboratory shall receive every consideration for their bodily comfort; they shall be kindly treated and properly fed; and their surroundings shall be kept in the best possible sanitary condition.

III. No operations on animals shall be made except with the sanction of the Director of the Laboratory, who holds himself responsible for the importance of the problems studied and for the propriety of the procedures used in the solution of these problems.

IV. In any operation likely to cause greater discomfort than that attending anesthetization, the animal shall first be rendered incapable of perceiving pain and shall be maintained in that condition until the operation is ended.

Exceptions to this rule will be made by the Director alone and then only when anesthesia would defeat the object of the experiment. In such cases an anesthetic shall be used as far as possible and may be discontinued only as long as is absolutely essential for the necessary observations.

V. At the conclusion of the experiment the animal shall be killed painlessly.

Exceptions to this rule will be made only when continuance of the animal's life is necessary to determine the result of the experiment. In that case, the same aseptic precautions shall be observed during the operation and as far as possible the same care shall be taken to minimize discomforts during the convalescence as in a hospital for human beings.

Thus, operations upon animals are conducted under anesthetics exactly as operations upon man, and the animals are equally well cared for. I know of no laboratory experiments on animals done today without general or local anesthesia which would not be done in the same man-

ner upon patients in hospitals. Neither investigators in the laboratories nor the doctors in the hospitals give anesthesia for the taking of blood specimens, for the passing of a stomach tube, for a lumbar puncture, or for like procedures. Moreover, further control exists by reason of the fact that no editor of a reputable medical journal will publish the results of experimental work if cruelty to the animals has unnecessarily occurred. And the profession of medicine itself frowns on work that does not protect carefully the experimental animals.

With this understanding we propose that the time has come for the more intelligent application of scientific labor for the improvement of our health and comfort. We need a law that gives unclaimed animals without cost or quarrel to reputable centers for medical study, such as our medical schools. Thus, at no financial outlay an adequate supply of animals would be available, funds previously spent for the purchase of animals would be released for greater efforts in combating disease, and those who labor daily for the public good would be encouraged to greater efforts by this attitude and this assistance. Further, the laws concerning unclaimed bodies must be changed in some states, making it mandatory with state institutions to turn over unclaimed bodies to the already prescribed institutions. Thus will a beneficial impulse be given to the betterment of public health.

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THE SURGICAL MANAGEMENT OF THE USUAL EXTRAHEPATIC BILIARY LESIONS

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SINCE the early days of elective surgery, diseases of the gall bladder and bile ducts have afforded the surgeon many interesting problems. The first bold attempts were directed toward the simple drainage of an acutely swollen gall bladder with the removal, if possible, of the stones within it. With the advent of satisfactory anesthesia, these operations were gradually replaced by extirpation of the inflamed structure. As surgical asepsis and technique improved, the interval removal of a gall bladder containing stones that had produced recurring attacks of inflammation or even colic became a common practice. The safety of simple drainage as opposed to cholecystectomy was a chief source of debate among surgeons a little over a quarter of a century ago. That those patients who survived the more radical operation were more likely to remain symptom free than those who had simple drainage was soon established. It did not take long to reverse the mortality figures since the drainage operations were reserved for the very ill or feeble patient, while cholecystectomy became a routine practice whenever feasible.

Operations on the common hepatic bile duct were undertaken only when symptoms and signs developed indicating a stone in the duct. These were usually after cholecystectomy had failed to bring relief and, practically, the only indication for duct exploration was jaundice that had followed biliary colic. As time and experience progressed, it became obvious that other signs and symptoms were indicative of duct pathology. We are now faced with the problem of exploring the ducts in a considerable proportion of primary operations on the biliary system. It has been shown that approximately 20 per cent of all patients now operated upon for stones or inflammation in the gall bladder also will have stones in the bile ducts. That many of these stones are small and pass through the papilla of Vater with or without pain is well established. It has been recognized, however, that the chance of having these duct stones produce symptoms requiring further surgery is likely. For this reason, the ducts should be explored at the primary procedure if the indications of trouble within them are evident; these are based on the history and physical signs present before operation, as well as the findings at the time the region is exposed.

Since diagnostic methods[1] have progressed to a point where positive evidence of biliary tract pathology can be made by the roentgenologist, operations at a time of election have become more frequent. Patients are now more willing to submit to elective surgery

and operations directed to relieve them are more readily undertaken by the surgeon. That any surgical procedure can be devoid of all danger is still a hope of the future; on the other hand, the evidence for or against elective surgery must be carefully weighed. An operation in the early stages of biliary tract disease often forestalls an urgent surgical need that may come in later months or years. This unavoidable surgical problem may be ten times as dangerous as an operation at a time of election and before the disease has caused damage to the liver, pancreas, and other neighboring structures. These factors have brought about an increase in operations on the gall bladder and ducts as soon as evidence is clear that these are diseased. Thus, it is important that these operations be undertaken in such a manner that fatalities will be rare and serious damage to vital structures will not often take place. One of the most tragic surgical accidents is injury of the common duct during cholecystectomy. These patients often do not die soon after the operation but remain alive as invalids for years. Restoration of the duct continuity becomes increasingly difficult as the weeks of hopeful waiting pass by.

This leads me to stress an operative technique that will be associated with very rare injury of the common or hepatic ducts or an accidental ligation of the hepatic artery. There are many anomalies of the ducts and, occasionally, the hepatic artery actually crosses the surface of common hepatic duct in a diagonal direction. In the dissection required to expose the cystic artery and cystic duct, there often occurs some bleeding; this may obscure the anatomy of this region to an extent that structures are mistaken one for the other. It is obvious one should never clamp and divide any vessel or duct under any circumstances that fail in the accurate identification of the cystic duct and artery and the common hepatic duct. In fully 50 per cent of the patients who are operated upon in the Massachusetts General Hospital for biliary tract disease, this dissection cannot be made with accuracy and safety if this part of the operation is undertaken while the gall bladder is still in place. Varying degrees of inflammatory reaction in this region and the contour of the patient account for this difficulty. That an experienced surgeon may safely make this dissection in nearly every instance without damage to nearby structures is admitted. That this is the method of cholecystectomy which should be taught, as the correct one, to younger surgeons is strongly questioned.

Cholecystectomy from the fundus toward the ducts is an old procedure. As a matter of fact, probably all of the early operations were carried out in this manner. Anatomical dissection from the ducts toward the fundus is a natural result of the more accurate knowledge of anatomy by the operating surgeon and his correct effort to secure the blood supply before the removal of any part. When exposure is ideal, this type of operation simplifies the procedure of cholecystec-

tomy. Division of the cystic artery decreases the bleeding during the remaining dissection. Unfortunately, such a procedure frequently results in the removal of that portion of the fibrous capsule of Glisson that protects the liver. If this is lost, closure of the raw liver surface is difficult and there is considerable seepage from small bile sinuses as well as from veins in this area. It is easy to forget that there is no cystic vein accompanying the artery. The venous return from the gall bladder is through multiple small veins going directly into the liver. The need of attention to the liver bed has caused Thorek[2] to recommend leaving the entire thickness of the gall bladder attached to the liver and destroying the mucous lining of this remaining segment by electrocoagulation. This, and other papers on the subject, would lead one to believe that it may be the usual custom of some surgeons to denude the liver bed when removing the gall bladder. It has long been a practice in our hospital and elsewhere to carefully preserve enough of the posterior serous coat and the fibrous capsule directly between the gall bladder and liver surface to peritonealize adequately this defect. This refinement is of great importance since often, when neglected, the duodenum becomes firmly fixed to this raw area by dense adhesions. Not only will such a complication frequently cause serious digestive symptoms, but the hazard of any future operation in this region is increased. I am convinced that this area should be left dry and that careful peritonealization is to be accomplished at all costs. This can be more easily arranged if the dissection is carried out from the fundus toward the ducts. The objection to the method is increased bleeding during the operation; this can be easily controlled by a painstaking ligation of the venous channels as they are exposed. Also, when small stones are present in the gall bladder, they on occasion may be forced through the cystic duct during the necessary manipulation of the gall bladder. It is often possible to isolate the cystic artery and duct at the beginning of the operation and place upon them temporary clamps. This obviates most of the objections and it immediately occurs to everyone that, having done this, why not carry out the dissection from below upward. The reasons are chiefly that in many instances these clamps will be found too near or too far away from the common duct and that actually they have not been placed where they should be for best results. Also, as stated above, it is frequently impossible to prevent a portion of the fibrous attachment from pulling away from the liver bed. Once it is detached, there will be a certain amount of bile and blood leakage from this denuded area in spite of any effort to combat it. That such may not interfere with a successful outcome is admitted, but serious complications can arise from this source.

We have all noticed the ease with which the peritoneal covering of the gall bladder can be separated from the underlying structures

during certain phases of inflammation. Having this in mind, it occurred to Rowley[3] to use artificial edema in the peritoneal covering of the chronic gall bladder and thus make the dissection easier. The principle for this aid in separating delicate tissues was probably first advocated by Bevan[4] in his article on the technique for operation on the undescended testicle. I have found this method so successful that now cholecystectomy from the fundus toward the ducts is a simple and satisfactory procedure; rarely is there any break in the continuity of the underlying muscular and mucous coats so that the operation progresses in an orderly fashion. Having freed the gall bladder well down to the ampulla and secured the venous communications, one then places a moist gauze pad in the liver bed and, by retraction in two directions, exposes the duct area accurately. Danger to the common duct and the hepatic artery is thus reduced to a minimum, since they are approached and visualized as they are directly exposed from above.

We have attempted to trace the type of operation done in every instance of damage to the common duct that has entered the Massachusetts General Hospital. In only one patient in this group was the duct injured when the operation had been carried out from the fundus toward the ducts. This indicates that the procedure we recommend is not entirely devoid of danger but that catastrophies are less likely to occur. It has been frequently stated that the questions of courage, knowledge, and skill are all at stake if one deviates from the so-called anatomical operation of cholecystectomy from the ducts toward the fundus. This attitude has caused many young surgeons to make an error in judgment in the presence of inflammatory reaction that would challenge the most experienced man in this field. Little has been said in recent years concerning a safe and orderly operation carried out as described above. We feel that it is wise to teach this method to the resident staff and urge them to carry out this procedure in easy cases at first, so that the technique will not be difficult for them when they are faced with the deeply placed, adherent, or inflamed gall bladder.

In our clinic there has been a run of 432 consecutive cholecystectomies in the past four years with 7 deaths, a mortality rate of 1.6 per cent. In the previous five-year period there were 22 deaths in 751 cholecystectomies, a mortality rate of 2.9 per cent, giving an average mortality rate for nine years of 2.45 per cent. Common duct explorations were carried out in conjunction with cholecystectomy in 35 per cent of patients operated upon between 1931 and 1939. During the past four years, this figure rose to 44.2 per cent. In this latter group stones were found in the ducts in 20.7 per cent of all the patients operated upon or less than one-half of the ducts explored. About 6 per cent more of these were found to have an abnormally tight sphincter of

Oddi. Thus, it is evident that common duct exploration was carried out about twice as often as was necessary. We have carefully studied the records in these cases to ascertain the indications for duct exploration and find it difficult to cite many instances where the procedure was unjustifiable. We did remove stones from a certain number of ducts of normal size or less when the indications were correct. In our series the most reliable symptom of common duct stone, other than jaundice, was frequency of attacks. In 66 patients who had attacks of pain as often as seven or less days apart, we found stones in the ducts

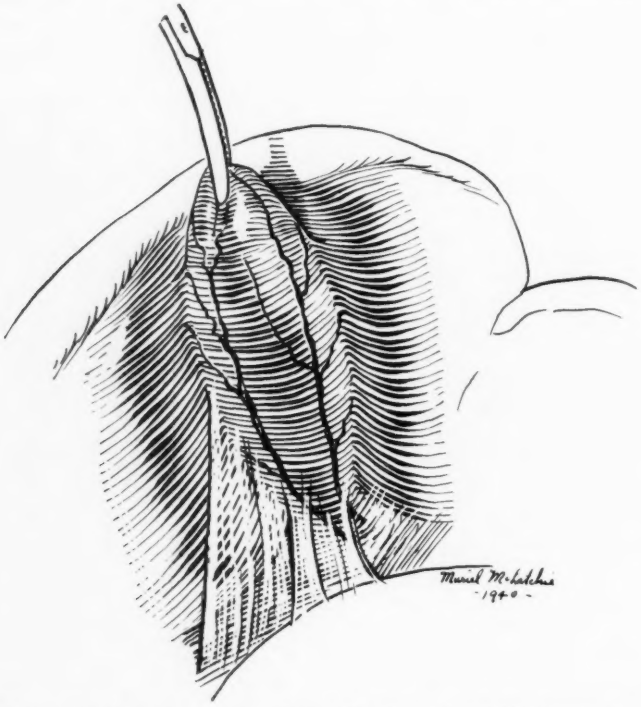

Fig. 1.—Schematic drawing representing adhesions about the lower segment of the gall bladder and bile ducts. This is a frequent finding and often under these circumstances the dissection required to expose the cystic duct and artery is accompanied by enough bleeding to obscure the field.

of 60. We are sure that one cannot depend on the size of the duct as an unmistakable criterion for stone within it. Inasmuch as the mortality rate was elevated to 4.25 per cent when duct exploration was superimposed on cholecystectomy, we felt that further analysis of this group was indicated. In those patients who had stones removed from the ducts at operation, the mortality was 7.16 per cent, while in those in whom no stones were found the mortality rate was 2.04 per cent. In other words, the careful exploration of the duct itself need not increase the risk, while the pathologic processes associated with common duct stone are significant of a more serious situation.

If we are to explore the ducts in a large proportion of routine primary operations on the biliary system, when the indications from the his-

tory or operative findings are correct, we will have to expect a high percentage of negative explorations. On the other hand, we will overlook stones in the ducts of many patients who will continue to have symptoms if we do not investigate the ducts when there is reasonable evidence that a stone or a constricted papilla exists. With this in mind, we must standardize our duct explorations in such a manner that this added procedure does not increase the danger out of propor-

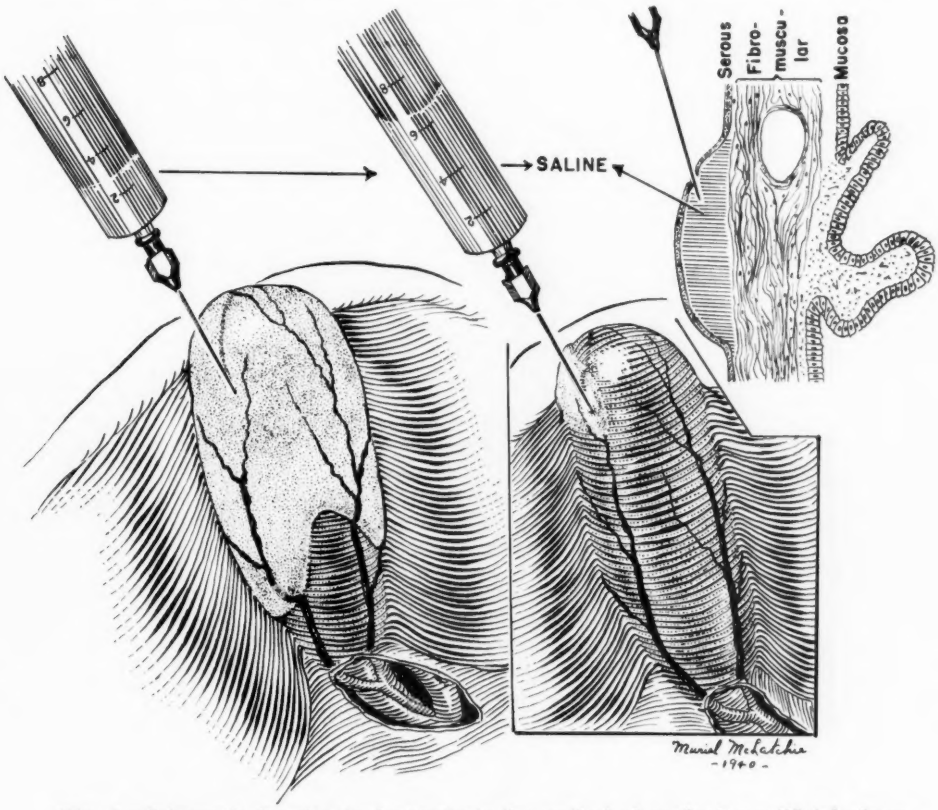

Fig. 2.—Schematic drawing to demonstrate the method of producing artificial edema of the gall bladder wall. Sterile water, salt solution, or novocain solution may be used. Temporary clamps placed on the cystic artery and duct decrease the bleeding and prevent small stones from being manipulated into the common duct during the dissection. These are unimportant features and such clamps should be cautiously placed. The inset shows by cross section a small segment of the wall of the gall bladder indicating the ideal cleavage plane in which to introduce the fluid. The artificial edema outlines the blood vessels more clearly. The incision through the peritoneal surface can be made into this edematous area with little danger of penetrating the deeper coats of the gall bladder.

tion to the rewards for such interference. In our hands this is carried out in a systematic fashion. Perfect exposure of a segment of the supraduodenal portion of the duct must be obtained. Usually, it is wise to free the outer attachments of the duodenum so that this structure can be rolled toward the median line. The duct is aspirated with a fine hypodermic needle, an important precaution regardless of the appearance of the bile withdrawn. When possible, the common duct is opened distal to the cystic duct, but there is great variation in the

length and entrance of this duct into the common duct. One should estimate the size of the duct and make a longitudinal incision in it not longer than the diameter of the duct itself. This wound is best held apart by fine silk guy sutures since these cause less trauma than instruments devised for this purpose. It is wise to culture the bile that escapes from the open duct since subsequent infection, if it should develop, may be more intelligently treated. The escaping bile should

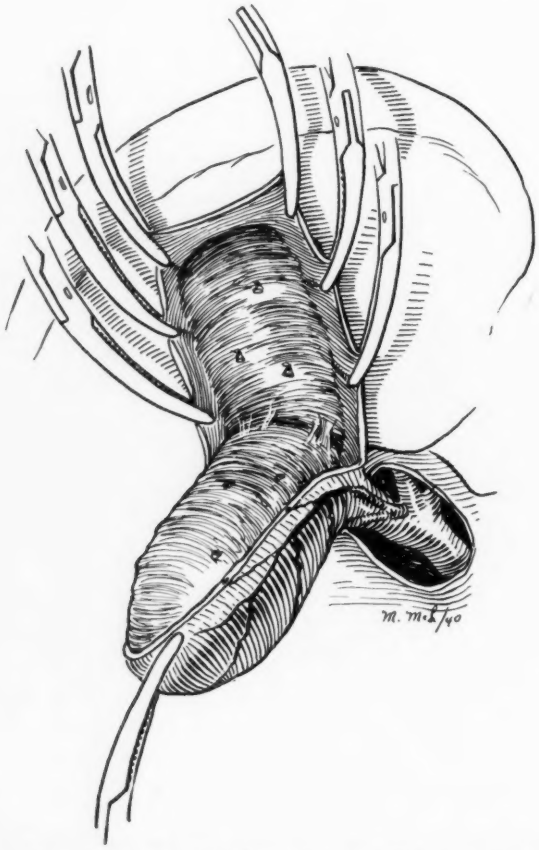

Fig. 3.—As the dissection is carried down between the muscularis of the posterior wall of the gall bladder and the fibrous capsule of Glisson, the small venous sinuses can be secured and ligated. At this point or in most instances after the dissection has been carried further toward the ampulla, a moist gauze sponge is placed against the liver and retraction made by a second assistant.

be picked up with a suction tip. I have found it of great advantage, at this stage of the operation, to go to the left side of the patient so that, by placing two fingers of the left hand in the foramen of Winslow, I can palpate the region of the ducts more satisfactorily. Instruments can be handled under vision and guided by touch. After removing the obvious stones by milking them from the ducts into the incision, one then may use long curved stone forceps to advantage. Smooth scoops or brain spoons will aid in the removal of small stones, fragments, and

detritus. The ducts may be irrigated with normal salt solution to better advantage after the next step, which we feel is so important.

Many surgeons have felt for years that it was wise to ascertain the patency of the duct outlet. A considerable number have become conscious of the need for more than this. The gradual, careful dilatation of the papilla of Vater has become increasingly more popular. The rationale of such a maneuver is based on the frequent findings of a very tight outlet and subsequent symptoms if dilatation has been omitted. Warnings have been issued concerning the danger of such a practice, but, if it is carried out in a logical manner, these dangers are minimal.

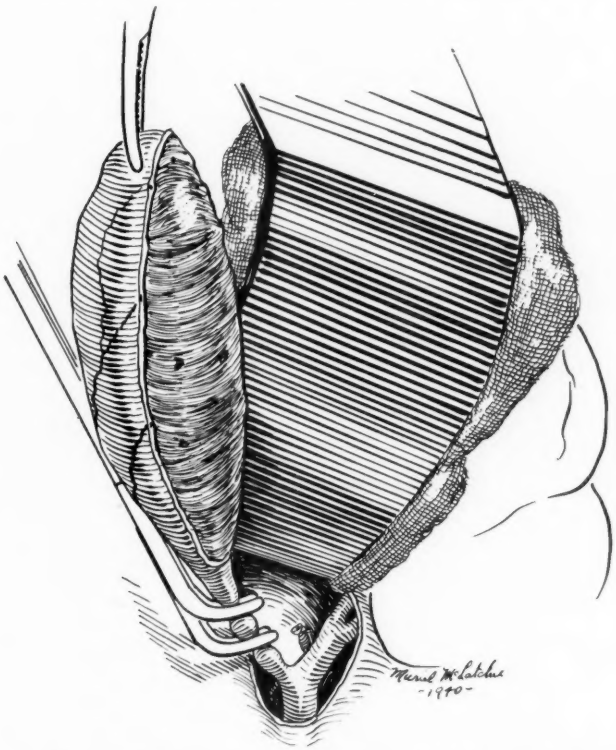

Fig. 4.—The pad protecting the liver has been moved downward so that the entire right lobe can be held out of the way. The ducts are carefully palpated for stone and great care is used not to leave a stone in the stump of the cystic duct.

In our hospital there has been a gradual adoption of routine instrumentation of the papilla of Vater whenever the ducts were explored. We have approached this feature of the operative technique[5] with caution and after some experimental evidence indicated that serious damage did not occur. During the five-year period between 1930 and 1935, 395 ducts were explored; of these, 231 had dilatation of the papilla of Vater, while in 164 no dilatation was done. In the next four years 380 ducts were explored with dilatation of the papilla carried out in all but 50 cases. The operative mortality averaged a little over 1 per cent greater

in those patients not having dilatation of the papilla. This may be partially coincidence or possibly some of the patients not having dilatation were more ill and the surgeon elected to omit this procedure. The increased morbidity, however, in the nondilated group is very striking. This apparently substantiates the claim that many patients need this stretching of the duct outlet to allow for the early unrestricted flow of bile into the duodenum. (Table I.) Eight of the 561 patients having dilatation of the papilla came to secondary operation on the duct at some later period. In 4 of these stones were again found in the ducts and

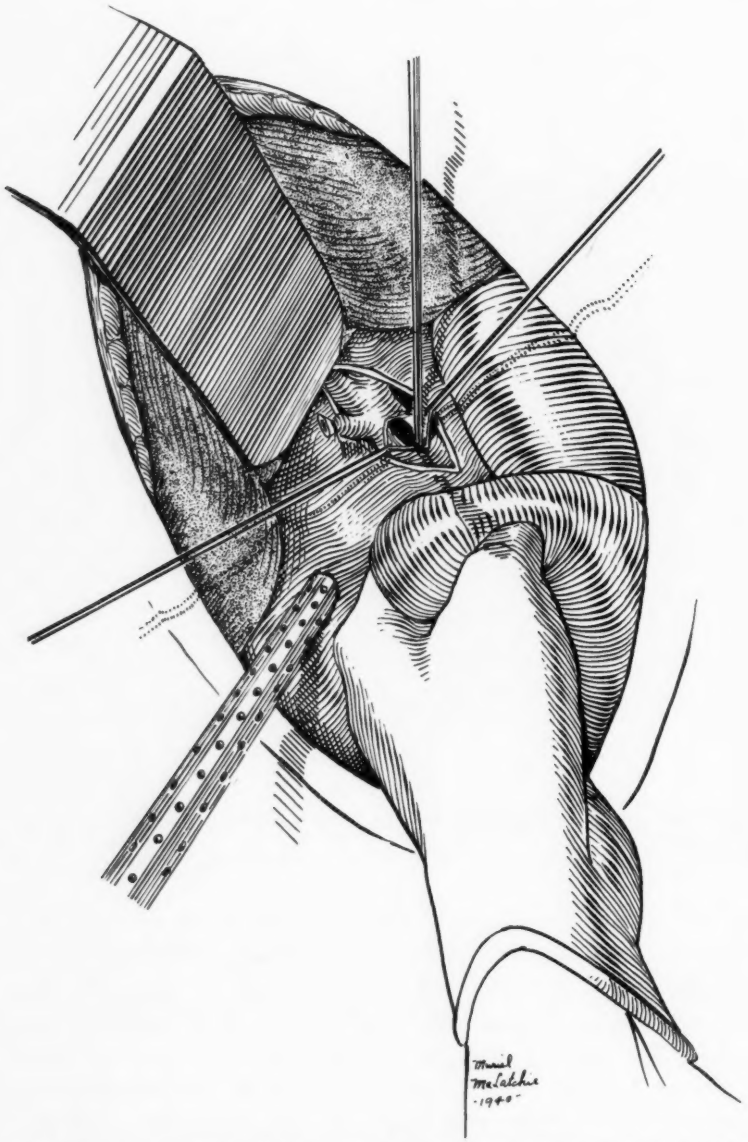

Fig. 5.—Schematic drawing indicating the method of instrumentation of the duct and papilla. The operator is standing on the patient's left. The ease of manipulation of the instruments from this position often simplifies the procedure.

in 2 instances recorded the papilla was found to be the same size to which it had been dilated at the first operation. One other patient in this group had four attacks of biliary colic after leaving the hospital but has been symptom-free for a subsequent period of three and one-half years. In the 214 patients who did not have the papilla dilated, there were 11 secondary operations with stones found in 9. Ten other patients in this group continued to have symptoms indicative of stone or dyskinesia but were not reoperated upon in our clinic. Thus, there

Fig. 6.—The anterior abdominal wall is left out of this sketch to give a better idea of the relationship of the wick and the tube from the common duct to surrounding structures. It is important to see that bile is draining from the common duct tube before the abdomen is closed. Stab wounds for drainage are helpful in thin patients in whom a vertical incision has been made. This additional wound should be placed well below the twelfth rib and the wick placed in Morrison's pouch under direct vision. Obese patients with a wide costal angle do better with a transverse incision.

TABLE I

REASONS FOR PROLONGED HOSPITALIZATION

PAPILLA	DILATED (561 CASES)	NOT DILATED (214 CASES)
Wound sepsis	29	18
Pulmonary complications	9	2
Prolonged biliary drainage	4	27
Bile peritonitis	4	1
Study for other diseases	4	
Dehiscence	3	1
Miscellaneous	8	5
Totals	61	54
Percentage of total operations	10.9	25.7

is this evidence that routine dilatation of the papilla reduces the chance of continued or recurrent symptoms from approximately 10 per cent to less than 2 per cent. In none of our cases has there been evidence of cicatricial obstruction to the duct outlet after dilatation. Duodenal reflux has occurred only once after this procedure with spontaneous recovery in twenty-one days. We have not been unfortunate enough to precipitate a serious acute ascending infection.[6]

There are a variety of methods for dilating the duct outlet. Cheever[7] described the use of woven silk Coudé urethral catheters for this purpose. Walters and Snell[8] prefer long, smooth, graduated scoops. Mixter[9] has devised an ingenious hollow metal dilator which allows the injection of irrigating fluid through it. Various urethral sounds and bougies have been advocated. Bakeš[10] made some elongated olive-tip metal bougies with malleable handles; these are graduated from 3 mm. upward, with each larger size only 1 mm. greater in diameter. We have found these dilators satisfactory and they have the advantage of being easily sterilized and always at hand. One should never attempt to stretch the duct itself. If the size of the duct is measured by the dilator, one should never use an instrument of greater diameter. The instrumentation of the papilla should be carried out without force and rarely should the dilatation exceed that of the estimated diameter of the hepatic ducts. The average dilatation in our cases was 7 mm. In the small-sized ducts one may wish to use the largest dilator that will enter the duct without stretching it in order to obtain the maximum opening into the duodenum. In the very large ducts one may feel that stones can remain in the hepatic ducts after all reasonable efforts have been made to remove them. In such an instance provision may be made for their passage into the duodenum by stretching the papilla to a size comparable to that of other stones found within the ducts or to that of the diameter of the hepatic ducts; occasionally, this requires the use of the larger sized dilators.

Disturbance of the sphincteric action of the papilla of Vater has been frowned upon by some investigators. It has been stated that serious sequelae, such as indigestion and ascending infection, may occur. Comparison has been made between this disturbance of the sphincter by dilatation and the results obtained following surgical anastomosis of the duct to the duodenum. We have considerable clinical evidence that the average dilatation of 7 mm. does not produce either of these complications. Cheever felt that the human papilla could be gradually dilated to this degree without permanent interference with its function. Perhaps the analogy may warrant criticism, but every surgeon knows the extent to which the sphincter ani can be dilated without disaster. We have followed those patients who have

had large ducts with dilatations of the outlet above the average size. We must take into consideration the fact that such individuals have liver damage and permanently dilated and usually infected hepatic ducts at the time of operation. The dilatation of the biliary tree has been a gradual process. Perhaps, they have developed a certain immunity to the bacterial flora of the upper gastrointestinal tract. Possibly, their apparent good health after operation was subjectively one of comparison to their previous state. At any rate, we found no evidence that dilatation of the duct outlet to a size comparable to that of their hepatic ducts resulted in any serious sequelae. I believe that such a dilatation is not comparable to surgical anastomosis between the duct and the

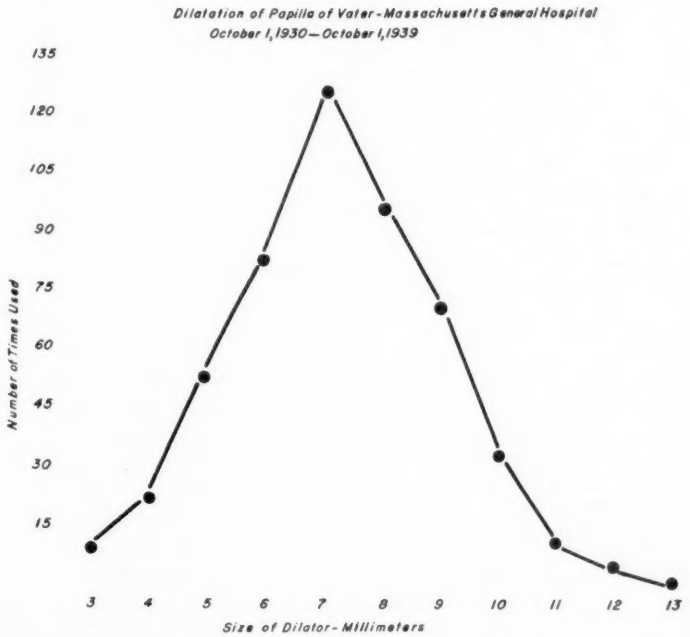

Fig. 7.—Showing the average dilatation of the papilla of Vater in 561 consecutive cases.

duodenum. In the first place, the direction and place of entrance are unchanged from those provided by nature. Also, one must bear in mind the oblique direction of the duct through the wall of the duodenum. This makes it likely that some valvelike action of the duodenal mucosa may exist after the sphincter has been destroyed.

Bakeš believed that the duct outlet remained the size to which it was dilated for an indefinite period and possibly permanently. This opinion was chiefly based on two patients in both of whom the dilatation had been carried to over 1 cm. In two of our patients having secondary duct exploration for stone, the papilla was found to admit the same size dilator that was used in the first operation. These were 8 and 9 mm. respectively. I can offer no satisfactory theory as to how stones of such

caliber can form in the duct itself without having passed through the previously dilated papilla before they had reached a size larger than the diameter of the outlet. Long respites from symptoms between operations indicate that these stones, as such, were not overlooked at the previous operation. Remaining fragments in the cystic duct, pancreas, or wall of the duct to act as a nucleus, sluggish bile currents, and duct diverticula are some of the possibilities that occur to us. It seems unlikely that dilatation of the sphincter within its physiologic limits could be expected to result in a permanent increase in its diameter. It is important, however, to observe the small percentage of such patients having future symptoms, and also, the fact that there has not been a single instance of any evidence of cicatricial constriction of the duct outlet following the method. Doubtless, one could cause sufficient trauma to this area to result in serious scar formation even if the instrumentation was done from within the duct. It is evident that such trauma could be accomplished more effectively if the instrumentation was made in reverse fashion through an opening in the duodenum. Deductions from animal experiments along this line are difficult to evaluate since one cannot reproduce the various pathologic processes found in the human biliary system.

Drainage of an explored duct is wise in all instances, since a safety valve of this nature aids in the control of liver decompression; it also gives some information regarding the character and quantity of the bile secreted. The best reason for drainage, however, is based on the difficulty of accurate closure of the incision in the average duct without narrowing it. In very large ducts one may feel more secure about effecting a water-tight suture line and, occasionally, in such a case omission of the tube might be justified. When stones are known to remain in the hepatic ducts, it seems desirable to avail oneself of any effect from hydrostatic pressure within the biliary system. With a dilated papilla in a large duct, this may not be influenced by closure of the incision to any great extent; still, it eliminates the tube which may prevent stones from passing by it. After dilatation of the duct outlet, one does not need prolonged external drainage since the bile will flow freely into the duodenum in all cases as soon as any reactionary edema from the manipulation has subsided. It was found that external drainage ceased almost at once when the tube was removed at the end of ten days in our patients who had had dilatation of the papilla. When the papilla was not dilated, prolonged external drainage of bile occurred after removal of the tube in many cases.

It probably matters very little what type of tube is used to drain the common duct. Many surgeons still prefer the routine use of the T-tube and this is a satisfactory method. It should always be used after reconstruction operations upon the duct and when prolonged

external drainage is desired. This type of tube, however, does offer considerable resistance to removal and doubtless produces some trauma to the duct. In routine cases we have found a No. 10 or 12 French whistle-tipped catheter entirely satisfactory. It should be of live rubber and the suture passing through it should not weaken the tube enough for it to break at the time of removal nor should the suture pass entirely through its lumen. In small ducts it is well to point the end of the tube toward the liver. In large ducts its direction is of less importance, but there are some advantages in pointing it toward the duodenum, chiefly because this direction may cause less collection of debris in the current of bile and thereby enhances the passage of an overlooked stone. Whatever type of tube one uses, it is imperative to ascertain that bile is flowing freely through it before closing the abdomen. If this precaution is followed, there will be few cases of bile peritonitis following duct exploration. If, by chance, one finds at the end of a few hours that no bile is coming from the tube but that the dressings are saturated, then one must assume that bile peritonitis will result. If little or no bile is coming from either tube or drain at the end of twenty-four hours, the resultant discomfort, restlessness, and rapid pulse in such a patient will indicate bile peritonitis. The mortality from such a complication is high, approximately 25 cent, while those who survive have a stormy convalescence. Although it is difficult for a surgeon to admit that there is a mechanical fault in his technique, under these circumstances he should correct this error at the earliest possible moment. By a rearrangement of the drainage in the early hours after operation, a fatality may be prevented and in every instance an easier convalescence obtained. If one waits until the manifestations of full-blown bile peritonitis have developed, the risk of secondary operations is much greater; after forty-eight hours the risk of operation usually outweighs its rewards. Bile collects above the liver in considerable quantities and this in itself creates a difficult problem and from its pressure on the diaphragm, may have some influence on the end result.

It is well to establish drainage of the most dependent part of this region of the abdominal cavity by cigarette wick or soft rubber tube, regardless of whether or not the common duct has been explored, although by taking great pains one may feel secure in many instances in not leaving a wick through the abdominal wall. Doubtless, long series of successful operations on the biliary system without drainage can be reported. Once in a great while, however, one is greatly comforted by the presence of such a tube. An accessory duct may have been overlooked and may produce enough bile drainage to create a serious problem. In spite of great care an occasional tie will slip off the cystic duct. Rarely, there is late bleeding of a quantity difficult for nature to absorb. When drains are properly placed through

a small stab wound, the original incision is not influenced by a foreign body. This is further obviated by the transverse incision, in which case the outer end of the wound may allow for drainage in an ideal manner. Drainage should be established to the subhepatic space described by Morison[11] since this is the most dependent area in the right upper quadrant. If one uses a longitudinal incision or any of its modifications and attempts to establish drainage from this deep pocket through the incisional wound, the drain must be very long. The drains have a tendency to be lifted out of the ideal position if any distention of the abdomen takes place after operation. Such foreign bodies passing through the incision are conducive to wound infection and subsequent hernia in scar. If one adopts the method of a short wick directly to the area by which all drainage from the biliary tract area must pass or collect, great care must be taken that the counter incision is accurately made. The wicks must be placed under vision and not by touch alone. It is best not to use such a method in obese individuals and usually not in secondary operations. In the former, this tunnel through the fat may be too narrow to allow for the adequate escape of material along its course. In the latter, adhesions between the liver and parietal peritoneum or to the hepatic flexure of the colon may interfere with the establishment of ideal drainage since the subhepatic space itself may be obliterated. In the average patient, however, one finds the convalescence materially shortened by the accurate establishment of a short drain through the abdominal wall directly into this subhepatic pocket. This eliminates wound contamination and creates little disturbance on removal. It doubtless causes fewer adhesions in the region of the operative field and further reduces the chances of duodenal irritation. In our cases there has been no evidence that stab wound drainage increases the risk of bile peritonitis or subdiaphragmatic abscess.

SUMMARY AND CONCLUSIONS

1. A simple and satisfactory method of cholecystectomy from the fundus toward the ducts is presented. The safety of this method is stressed.

2. Exploration of the common hepatic duct should be carried out in conjunction with cholecystectomy in a high percentage of cases. The indications for duct exploration should be carefully determined in each instance.

3. Routine dilatation of the papilla of Vater in common duct exploration is advocated. The morbidity is lowered and secondary operations are rarely necessary when this procedure is carried out.

4. If the duct is opened, it should usually be drained by a suitable tube.

5. The region of the operative field should be drained after nearly all operations upon the biliary system.

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THE PROTECTION OF THE LIVER FROM INJURY

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IT WAS not long after the demonstration by Simpson of chloroform as an anesthetic agent that it was found that necrosis of the liver at times followed its use.[1] The work and concepts of Rosenfeld[2] led to the suggestion that the administration of glucose might be of value not only in the prevention, but also in the treatment of hepatic necrosis induced by chloroform anesthesia. Rosenfeld[2] stated, in fact, that the detoxifying power of the liver *(entgiftenden Fähigkeiten)* is the greater the richer its content of carbohydrate.

In 1908 Wells[3] offered an acceptable explanation of the greatly increased susceptibility of the fatty liver to damage by chloroform. The clinical observation that chloroform particularly affected fatty livers when added to the well-known solubility of chloroform in fats led Wells to state: "It would seem probable, therefore, that a fatty liver would abstract much more chloroform from the blood than a normal liver, and that this chloroform would thus act more strongly and for a longer time on the protoplasm of the fatty liver cells than it would in a normal liver."

That a diet high in carbohydrate is protective and that a diet high in fat induces maximal susceptibility of the hepatic parenchyma when the liver is exposed to chloroform has been repeatedly confirmed since first reported in this country by Opie and Alford.[4] Diets rich in protein have also been found to be of value in protecting the liver against such injury, although their exact value has not been uniformly agreed upon. Starvation also markedly increases the susceptibility of hepatic parenchyma to injury by chloroform and various fat-soluble agents.

These experimental studies and their confirmation by Davis, Hall, and Whipple,[5] Graham,[6] and others led surgeons to believe that a high concentration of hepatic glycogen in itself would protect the liver from injury during operation and anesthesia, and furthermore that a high carbohydrate dietary was the most satisfactory means, subsequent to operation, of providing conditions conducive to hepatic cellular repair.

Davis, Hall, and Whipple[5] had reported that under the favorable circumstances of a high carbohydrate diet the liver could regenerate itself at the rate of nearly 100 Gm. of liver tissue a day. They also showed that the urinary nitrogen excretion was greatly increased following chloroform anesthesia and that, while this was accentuated in the

fasting animal, it was greatly decreased when glucose was administered during the postanesthetic period.

It was not long before emphasis on the intravenous injection of glucose as a pre- and postoperative measure in poor surgical risks presenting lesions of the biliary apparatus replaced emphasis on a high carbohydrate dietary. Eleven years ago I stated: "In many clinics the administration of dextrose is merely a routine procedure and little thought is given to the objects to be attained by its use. . . . If glycogen can be deposited, can this be done more readily by the intravenous injection of dextrose or can it be as easily attained by the ingestion of a high carbohydrate diet?"[7]

The rich carbohydrate diet which we used in the experiments reported eleven years ago contained approximately 80 per cent of carbohydrate and 20 per cent of protein. We were led to conclude that: "The liver cells regenerate rapidly on a high carbohydrate diet. They will not regenerate to the same extent on a diet low in carbohydrate."

TABLE I

DIET	CONTROL		EXPERIMENTAL APPORTIONMENT OF LIVER DAMAGE		
	AVERAGE LIVER GLYCOGEN (GM. %)	AVERAGE LIVER FATTY ACIDS (GM. %)	DEGENERATION (%)	NECROSIS (%)	TOTAL DAMAGED (%)
*Liver Damage at Ascending Fat Levels**					
Low fat	4.9	10.5	13	8	21
Medium fat	4.5	24.1	29	63	92
High fat	3.7	49.7	3	97	100
Liver Damage at High and Low Glycogen Levels					
High glycogen	6.2	18.4	13	49	62
Low glycogen	2.0	19.3	40	31	71

*Thirty or more rats in each group.

Evidence which Goldschmidt, Vars, and I have recently published[8] has led us to conclude that the incidence and severity of the damage to hepatic cells, following chloroform anesthesia, increase progressively with an increase in the concentration of lipid in the liver (Table I). Regardless of the concentration of glycogen in the liver at the time of anesthetization, the findings demonstrate that increasing lipid concentrations of the liver increase its susceptibility to chloroform. While the concentration of glycogen per se had no influence in modifying the incidence or the severity of the injury, this could be modified by the protein content of the ration fed for some days prior to anesthetization for the incidence of necrosis was but 50 per cent as high when a high protein diet was given (Table II). To recapitulate, a high concentration of hepatic glycogen per se failed to confer any discernible protection against the hepatotoxic action of chloroform in rats with the same concentration of hepatic lipid and a similar intake of protein in the diet.

These data, striking as they are, force us to modify our concept of the mechanism by which carbohydrate may provide protection against certain hepatotoxic agents and have led to further investigations, the results of which are of considerable importance in this field of therapy.

We were led to conclude, after reviewing the evidence, that the chief reason for the protection against hepatic injury following a high carbohydrate diet is probably the reduction in the lipid content of the liver which results from such a diet. Furthermore, under certain conditions, such as inanition, the administration of carbohydrate probably also protects the liver by virtue of its protein-sparing action. Thus the protective action of carbohydrate is purely an indirect one.

TABLE II

LIVER DAMAGE ON HIGH AND LOW PROTEIN DIETS (RATS)

DIET	CONTROL		EXPERIMENTAL APPORTIONMENT OF LIVER DAMAGE		
	AVERAGE LIVER GLYCOGEN (GM. %)	AVERAGE LIVER FATTY ACIDS (GM. %)	DEGENERATION (%)	NECROSIS (%)	TOTAL DAMAGED (%)
High protein	1.9	22.3	43	41	84
Low protein	6.9	23.5	6	88	94

In contrast to this, a diet containing an adequate amount of protein (17 per cent of the total calories) was found markedly to reduce the incidence and degree of hepatic necrosis, even in livers with a high lipid content. Less than one-half the animals on a high protein intake had liver necrosis (Table II). The protective action of protein in these experiments was not associated with the marked lipotropic action of protein which has been shown by Channon and Wilkinson,[9] for comparisons were made in animals with similar hepatic lipid concentrations. Thus, an adequate amount of protein in the dietary would appear to protect the liver both as the result of some intrinsic property of the protein itself and because the administration of an adequate amount of protein leads to a reduction in the content of hepatic lipid.

The increased susceptibility of the liver of the starved animal, we believe, is principally due to its depleted protein stores. The question of protein storage in the body, following the administration of a diet high in protein, is of particular importance if we assume that the protection conferred by such a diet is due to the protein per se. Whether the protein is stored in the sense that carbohydrate and fat are stored in the liver, or whether it is elaborated into hepatic or other tissue, it serves to protect the cells or replenish a structure which is being attacked.

Regardless of whether or not Whipple's concept[10] of "labile protein stores" proves finally to be acceptable, it is of interest that investigators in the field of protein storage have invariably directed their efforts

to the liver as the most probable repository for protein. Luck[11] has found that the total protein content of the liver, as well as the amount per unit of weight, is increased in those animals fed a high protein diet over those fed a low protein diet. Addis, Poo, and Lew,[12] in a study of the loss of protein from various tissues during a fast, found that the liver loses much more of its original protein content than any other organ. This fact "suggested that it [the liver] may be a depot for stored protein and that this special sort of protein may be used during fasting in much the same manner as glycogen is used during a fast."

From our own data and the support obtained from investigators in somewhat related fields, we have concluded that a liver high in lipid content and low in readily available protein is maximally susceptible to chloroform; while a liver low in lipid content and high in readily available protein is maximally resistant to injury by this agent.

The problem that confronts us is how best to induce conditions in the liver favorable to resistance to hepatotoxic agents on the one hand and to facilitate repair on the other. Such a liver should be low in lipid content and contain adequate amounts of protein.

Johnson, Vars, Zintel, and I[13] have shown that this condition is best brought about, in dogs, with common duct obstruction and cholecystectomy by a diet consisting of approximately 28 per cent of protein and 72 per cent of carbohydrate. These later experiments have illustrated the fact that not only is a diet of suitable composition of importance but it is equally important that the total caloric intake be adequate (Table III).

With a similar total caloric intake in both the high carbohydrate-low protein and the high carbohydrate-high protein diets the lipid concentration of the liver is reduced similar amounts in half the time when adequate protein is ingested. Furthermore, with such a diet the glycogen deposition in the liver reaches the highest levels obtained in our experiments.

The presence of a high protein content in the diet makes it possible for considerable amounts of fat to be ingested and still reduce the original lipid concentration in the liver. These experiments again and again point out the fact that diet and total caloric intake are important, for one without the other will not bring about the desired effects. In view of these data it seems hardly possible that we shall continue to place emphasis on the intravenous injection of glucose. Under the most favorable conditions of such therapy one can hardly provide more than 1,200 calories per day and this cannot be continued over long periods.

If the objects we wish to attain are to be achieved, they cannot be accomplished by providing but two-thirds of the calories necessary for basal energy requirements. A suitable program requires alimentary feeding, for only in this way can one provide for the basal requirements

TABLE III

EFFECT OF DIET ON LIVER FAT IN PRESENCE OF COMMON DUCT OBSTRUCTION

DIET	WEIGHT			DAYS ON DIET	CALORIES			CALORIES KG./DAY	LIVER GLYCOGEN		LIVER FATTY ACID		
	INITIAL	OPERATIVE	TERMINAL		PROTEIN (GM. %)	FAT (GM. %)	CARBOHYDRATE (GM. %)		OPERATIVE (GM. %)	TERMINAL (GM. %)	OPERATIVE (GM. %)	TERMINAL (GM. %)	CHANGE (GM. %)
High protein carbohydrate (7 dogs)	7.2	8.9	8.8	7	28	0	72	90	2.1	8.9	29.2	14.1	–54
High carbohydrate (4 dogs)	7.2	7.5	6.3	14	8	12	80	89	2.2	5.4	30.9	15.5	–48

and an additional amount of carbohydrate and protein for storage. While intravenously injected glucose may be used to reinforce oral feeding, it cannot now completely replace it. The glucose administered intravenously will protect the patient's stores of foodstuffs to the extent of 600 to 1,200 calories per day, depending upon whether a 5 or a 10 per cent solution of glucose is injected. Such therapy, however, will not lead to a marked prolonged deposition of glycogen in the liver for, even though it is temporarily deposited, it will be rapidly utilized for the energy requirements of the patient. Several years ago we examined histologically sections of the liver removed at operation under spinal anesthesia from patients who had received a 5 per cent glucose solution intravenously for a number of days prior to the operation. In those patients who received no food by mouth during the period of intravenous therapy the glycogen in the liver was always low and approximately one-third of the patients had large accumulations of hepatic lipid.

We have recently begun to reinvestigate more thoroughly the relationship between intravenous glucose administration and diet and liver composition in man. We have again been surprised at the frequency with which by analytical methods we have found high concentrations of lipid and low concentrations of glycogen in patients with biliary tract disease in whom during the preoperative period only intravenous therapy was administered. Only when a diet of adequate composition is given in sufficient calories can the liver of man be conditioned to minimal injury.

It is highly likely that many of the untoward reactions suffered by biliary tract patients after anesthesia and operation are due to varying degrees of degeneration or necrosis. If the lesion is of minor extent (Fig. 1), recovery can take place under favorable conditions, but when it is extensive death is inevitable (Fig. 2).

Bollman and Mann[14] have reported that the addition of considerable amounts of meat extract or of meat itself to dogs with experimental cirrhosis or long-standing obstructive jaundice results in the development of abdominal ascites. We have not found that the addition of protein, chiefly in the form of casein, but also partly as meat, resulted in the occurrence of ascites more frequently than when the casein was omitted from the diet. Messinger and Hawkins[15] have recently reported that they observed no untoward effects from the feeding of a meat diet to their dogs, even though they had severe liver injury.

From the results of our experiments, we believe that a high carbohydrate-high protein dietary will prove to be more efficacious in conditioning the liver to minimal injury than will a haphazard diet, a diet consisting of high carbohydrate-low protein, or the intravenous administration of glucose with little emphasis on the oral intake of food.

Soskin[16] has recently advanced arguments in favor of the intravenous administration of glucose where hepatic glycogen deposition is desired.

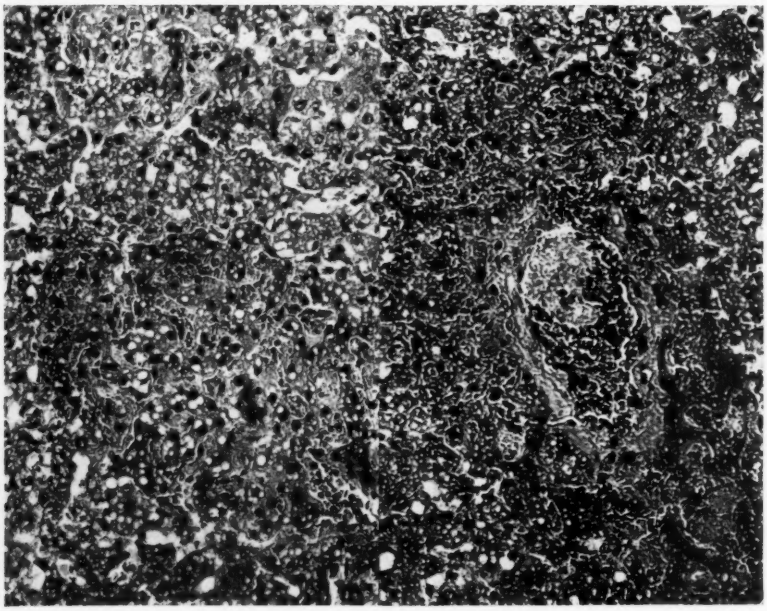

Fig. 1.—Minor necrosis of the liver following the use of ether anesthesia.

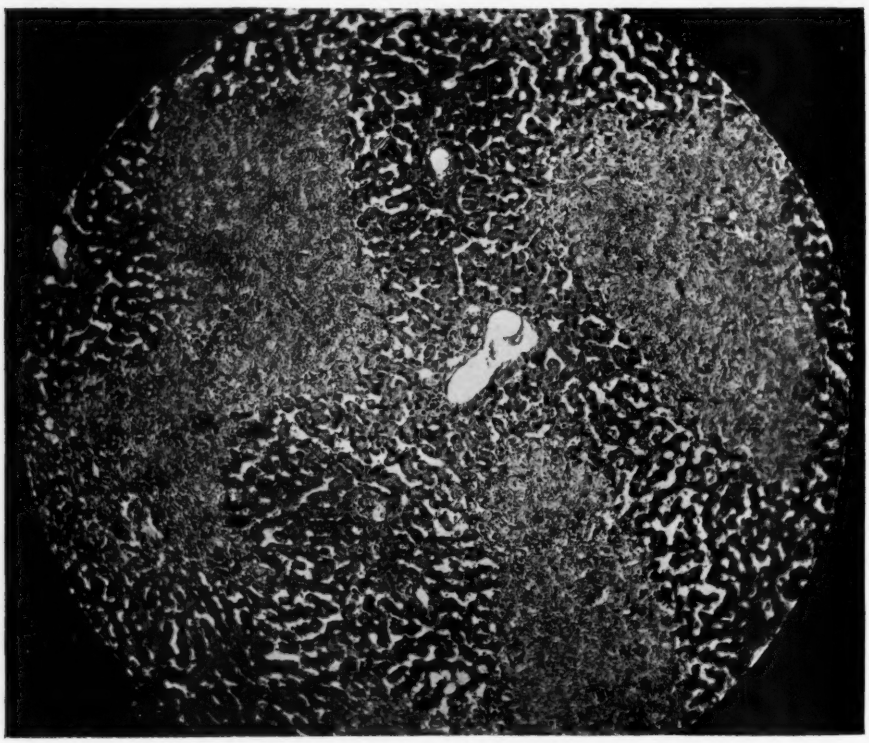

Fig. 2.—Extensive necrosis of the liver following anoxia.

Unless it becomes possible to introduce sufficient calories by this method alone or in conjunction with accessory methods of feeding the argument is without point for it is not possible to maintain the desired composition of the liver under conditions of undernutrition. The experiments we are now doing in man demonstrate that, unless an adequate caloric intake is maintained for some time prior to spinal anesthesia, glycogen deposition in man is not normal and hepatic lipid is not influenced. The amount of protein required for protection is not as yet known.

The diet, therefore, should not only be satisfactory from the standpoint of its composition, but it should be administered in sufficient amounts to insure an adequate caloric intake. The two factors can be looked upon as acting synergistically. It is not possible to outline the diet, for this must be done after consultation between dietitian and patient. It should consist of approximately 70 per cent carbohydrate, 25 per cent of protein, and not more than 5 per cent of fat in its caloric composition. From 2,500 to 3,500 calories should be given for several days prior to operation and resumed as soon as possible thereafter. If necessary the orojejunal method of feeding may be carried out. Since the oral route is at this time the only one by which a satisfactory diet of adequate caloric intake can be given it must remain the method of choice for the present. Only in those instances where oral feeding is not possible should parenteral feeding be depended upon.

Miller and Whipple[17] and Messinger and Hawkins[15] have confirmed our findings on the protective action of protein and the latter voice our sentiments when they state: "We suggest that in the face of liver injury a diet of protein and carbohydrate may prove to be of more value than carbohydrate alone."

Only with such a program in the pre- and postoperative periods can additional injury be prevented, or minimized, following anesthesia and operation and repair be facilitated during the period of recovery.

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THE INDICATIONS AND RESULTS OF PANCREATECTOMY FOR HYPOGLYCEMIA

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AFTER the discovery of insulin by Banting and Best[1] in 1922 and the later recognized effects of overdosage, Harris[2] in 1924 suggested a syndrome due to excessive secretion and action of insulin. Three years later Wilder and his associates[3] reported the first case of hyperinsulinism and hypoglycemia due to a carcinoma of the islet tissue of the pancreas operated upon by W. J. Mayo. Since that time world-wide interest has been excited in the varying clinical picture, the pathogenesis, and the treatment of spontaneous hypoglycemia. As a result it has been established that islet-cell tumor of the pancreas gives a characteristic triad of symptoms (Whipple):[4, 5] (1) attacks of nervous or gastrointestinal disturbances coming on in a fasting state associated with (2) a hypoglycemia with readings below 50 mg. per cent and (3) relieved immediately by ingestion of glucose. Unfortunately, the problem is complicated by the knowledge of the effect of the liver,[6] adrenals,[7] anterior lobe of the hypophysis,[8] thyroid, sympathetic nervous system,[9] and possibly other factors,[10, 11] on sugar metabolism and particularly their effect on the development of hypoglycemia. It is, therefore, obvious that before a surgical exploration of the pancreas is decided upon not only the symptom complex of hypoglycemia indicated by Whipple must be present but also lesions of the various ductless glands mentioned must be excluded by every possible chemical, physical, and therapeutic measure. The borderline cases should be treated conservatively, care being taken not to produce great adiposity by high sugar diet. The use of anterior lobe extracts of the hypophysis has not been encouraging to date.

As a result of careful selection of cases, Whipple[12] recently reported his own series of 19 tumors of islet tissue operatively removed from

TABLE I

PARTIAL RESECTION OF PANCREAS (TUMOR FOUND)

	NO. CASES	CURED	NO IMPROVEMENT	DIED
Adenoma	11*	8	1†	2
Carcinoma	4	2‡		2
Hamartoma	1	1		
	—	—	—	—
	16	11	1	4

*One patient had central nervous system damage.
†Patient had recurrent attacks after six months.
‡One patient well after four months; the other, after two months.

17 patients, and at the same time collected 65 other cases from the literature. Of these 82 cases, 65 had an islet-cell adenoma, 2 an atypical tumor, and 15 a carcinoma. There was an operative mortality of 13 patients, or 16 per cent. Of the 69 patients surviving the operation, 62 were cured of their hypoglycemia attacks and, of these, 36 had been followed for more than a year. This is truly an impressive report and would practically close the chapter were it not for the fact that a considerable number of patients have been operated upon with proper indications where no tumor of the pancreas has been found. This contingency has been considered by Whipple, who reported a group of 47 patients who had been explored (11) or whose pancreas had been more or less removed (36). Of these patients, 10 were cured, 7 improved, and 17 died postoperatively or later. A tumor was found at autopsy in 4, in the resected pancreas in 4, and at a second operation in 6. This would strongly imply that it is exceedingly hazardous to assume with careful selection of patients with hypoglycemia that a tumor of the islet cells is *not* present. This is sound reasoning as evidenced by 4 of Whipple's cases and 1 of Roscoe Graham's who had had resection of a portion of the pancreas without relief of symptoms and who at subsequent operations were found to have an adenoma of the islet cells in the head of the pancreas. Whipple also mentions 14 tumors of the pancreas overlooked at the first operation, 9 of which were found at a second operation and 5 at autopsy. Of these overlooked tumors, 7 were in the head, 5 in the tail, and 2 in the body of the pancreas.

This striking evidence for the probable presence of an islet tumor to explain spontaneous hypoglycemia of the type under discussion emphasizes the burden placed on the surgeon who not only must explore the body and tail of the pancreas but also should mobilize the duodenum, rotate it medially, and carefully examine the head of the pancreas before deciding that no tumor is present. Not all of these criteria of exploration have been carried out in the cases about to be discussed, but there have been reported a number of instances where, exploration of the pancreas failing to reveal a tumor, the surgeon has then decided upon a partial or subtotal removal of the pancreas with the hope that (1) a tumor might be found in the resected portion, (2) a hyperplasia of the islet cells might exist, or (3) removal of a considerable part of the pancreas, especially the tail and body, would cut down the insulin-secreting power of the organ.

In considering these collected cases of resection of the pancreas for hypoglycemia, the principal object has been to determine what course the surgeon has pursued when careful exploration of the pancreas failed to reveal a tumor of the pancreas and to attempt to lay down a principle of procedure based on the rather scanty literature on the subject. The cases coming under this classification would include: (1) partial resection of the pancreas, tumor found (14 cases); (2) subtotal resection of the pancreas, tumor found (3 cases); (3) subtotal resection of

TABLE II

PARTIAL RESECTION OF PANCREAS (TUMOR FOUND)

AUTHOR	PUBLICATION	AGE	DURATION SYMPTOMS	TYPE OF SYMPTOMS	MINIMUM BLOOD SUGAR	OPERATION	PATHOLOGY	RESULT
1. J. S. Tomkies	Texas State J. Med. **26**: 523, 1932.	30	3 yr.	Unconsciousness	41	Part of body and part of tail	Encapsulated adenoma	Symptom free 6 yr.
2. C. L. Derick et al.	New England J. Med. **268**: 243, 1933.	56	6 yr.	Coma	38	Tail resected	Adenoma in tail	Symptom free 5 yr.
3. E. A. Graham and N. A. Womack	Surg. Gynec. & Obst. 56, 728, 1933.	22	5 yr.	Petit mal confusion	25	4 cm. tail resected; nodule excised	Adenoma	No attacks; central nervous system damaged
4. A. O. Whipple (Case 5)	Ann. Surg. **101**: 1299, 1935.	28	6 yr.	Unconsciousness	28	Resection tail and part of body	2 adenomas	Symptom free 3 yr. 1 mo.
5. G. E. Cheley	Tr. West. S. A. **44**: 98, 1934.	50	13 yr.	Unconsciousness	30	Partial resection	Adenoma	Symptom free 3½ yr. except for exhaustion and amnesia
6. O. Wangensteen (Case 1)	Minnesota Med. **18**: 265, 1935.	28	3 yr.	Convulsions, unconsciousness	15.5	Resection tail	Adenoma	Symptom free 3 yr. 4 mo.
7. M. Munakata	Arch. f. klin Chir. **185**: 624-632, 1936.	40	14 mo.	Coma	33	Partial resection	Carcinoma epithelioma	Symptom free 4 mo.

8. E. J. Kepler and W. Walters	Proc. Staff Meet. Mayo Clin. **11**: 454, 1936.	46	2 yr.	Convulsions	35	Partial resection	Adenoma	Symptom free 2 yr. 4 mo.
9. E. Ziskind and W. A. Baley	J. Lab. & Clin. Med. **23**: 231, 1937.	38	2 yr.	Convulsions, mania	44	Exploration; no tumor; partial resection	2 adenomas	Died 32 hr. postoperatively
10. P. S. Federoff (Case 2)	Urach. gaz. **35**: 585-592, 1931.	16			Low	Partial resection	Carcinoma	Died
11. A. O. Whipple (Case 8)	Internat. S. J. **3**: 1, 1938.	51	1 yr.	Unconsciousness	54	Partial resection	Adenocarcinoma islet tissue	Died fifth day
12. M. Isaji	Frankfurt. Ztschr. f. Path. **53**: 178-207, 1939.	63		Unconsciousness	41	Partial resection 16 Gm. with tumor	Adenoma	Died second day
13. A. O. Whipple (Case 9)	J. Internat. Chir. **3**: 1, 1938.	45	8 mo.	Unconsciousness	26	Partial resection; excision	2 adenomas	Improved 2 mo.
14. A. O. Whipple (Case 10)	J. Internat. Chir. **3**: 1, 1938.	50	6 mo.	Convulsions	27	Partial resection	Carcinoma of islet tissue	Improved 2 mo.
15. T. Bailey and E. C. Cutler	J. Internat. Chir. **3**: 1, 1938.	56	17 mo.	Unconsciousness	31	Tail and part of body (14.5 Gm.)	Hamartoma	10 mo. no attacks
16. J. M. McCaughan and G. O. Brown (Case 4)	Ann. Surg. **105**: 354, 1937.	27		Convulsions	52	23 Gm. tail and body; exploration 2 mo. later	Islet adenoma tail	Improvement 6 mo.; recurrence of symptoms 6 mo. posteratively

TABLE III

PARTIAL RESECTION (NO TUMOR) NORMAL PANCREAS OR HYPERPLASIA

AUTHOR	PUBLICATION	AGE	DURATION SYMPTOMS	TYPE OF SYMPTOMS	MINIMUM BLOOD SUGAR	OPERATION	PATHOLOGY	RESULT
1. J. M. T. Finney and J. M. T. Finney, Jr.	Tr. Am. S. A. **46**: 268, 1928.	53	4 yr.	Unconsciousness	30	Resected 22.05 Gm.	Normal pancreas	Attacks continued
2. F. N. Allan et al.	J. A. M. A. **94**: 1116, 1930.	52	2 yr.	Stupor	40	Resection 14 Gm. tail and part body	Normal pancreas	No improvement
3. F. N. Allan et al.	J. A. M. A. **94**: 1116, 1930.	47	4 yr.	Convulsions	40	8 Gm. excised	Normal pancreas	No improvement
4. F. N. Allan et al.	J. A. M. A. **101**: 99, 1933.	42	1 yr.	Coma	40	8 Gm. tail excised	Normal pancreas	No permanent improvement
5. E. Holman et al.	Surg. Gynec. & Obst. **56**: 591, 1933.	31	2 yr.	Convulsions, coma	32	Resection; number Gm. not mentioned	Normal pancreas	No improvement
6. J. A. Evans and W. McDonough	J. Iowa M. Soc. **23**: 454, 1933.	41	1 yr.	Spells	?	Resection	Normal pancreas	No improvement
7. R. D. Forbes et al.	West. J. Surg. **47**: 76, 1939.	59		Unconsciousness	Low	9.5 Gm. tail	Hyperplasia (?) tumor	Blood sugar back to normal
8. H. Reid	Tr. West. S. A. **44**: 97, 1934.	22	8 yr.	Convulsions	60	Partial resection	Normal pancreas	Well except for slight attacks 4 yr. postoperatively
9. O. Wangensteen (Case 4)	Minnesota Med. **18**: 520-566, 1937.	29	9 mo.	Unconsciousness	46	(1) Excised tail; (2) exploration; (3) partial resection	Normal pancreas	Died sixth postoperative day

10. A. J. Berry	Brit. J. Surg. **33**: 51, 1935.	58	14 yr.	Convulsions	45	Partial resection 28 Gm.	Normal pancreas	Improved
11. L. Guerry and G. T. McCutchen	Ann. Surg. **104**: 602, 1936.	45	3 yr.	Convulsions	30	Resection	Normal pancreas	Died on operating table
12. O. Wangensteen (Case 5)	Minnesota Med. **20**: 566, 1927.	2½	2 yr.	Convulsions	23	Partial resection	Normal pancreas	Normal blood sugar; died 6 wk.; infection
13. A. F. Hurtman and J. C. Jandon (Case 18)	J. Pediat. **11**: 1, 1937.	1	9 mo.	Convulsions	6	Partial resection	Normal	Symptom free 4 yr.; mentally backward
14. J. A. Barnes and E. L. Richmond	New England J. Med. **213**: 225-228, 1935.			Unconsciousness, rigidity	30	Partial resection 2 inches tail	Normal pancreas	Died 3 days; pneumonia; no tumor found at autopsy
15. A. O. Whipple	J. Internat. Chir. **3**: 1, 1938.	25	6 mo.	Drowsy	35	Partial resection	Normal	Symptom free 1 yr. 9 mo.
16. J. McCaughan and G. O. Brown (Case 5)	Ann. Surg. **105**: 351, 1937.	50	3 yr.	Convulsions	62	Partial resection 5 Gm.	Hyperplasia	Some improvement
17. J. McCaughan and G. O. Brown (Case 1)	Ann. Surg. **105**: 351, 1937.	20	3 yr.	Convulsions	52	Partial resection 8 Gm.	Hyperplasia	Recurrent symptoms
18. J. McCaughan and G. O. Brown (Case 2)	Ann. Surg. **105**: 351, 1937.	17	4 yr.	Convulsions	45	Partial resection 22.5 Gm.	Normal pancreas	Recurrent symptoms

the pancreas, no tumor found, but subsequently found (4 cases); (4) partial resection of the pancreas, no tumor found, pancreas normal or hyperplasia of the islet tissue (19 cases); (5) subtotal resection of the pancreas, pancreas normal or hyperplasia of the islet tissue (17 cases).

It is difficult to decide arbitrarily what constitutes a partial and subtotal resection of the pancreas, many of the reports failing to state the exact number of grams of tissue removed. The size of the patient and the size of the pancreas also enter into the problem. Bailey and Cutler,[13] in discussing this matter, suggest that, inasmuch as the normal pancreas weighs between 60 and 90 Gm., at least four-fifths of the organ should be removed to constitute a subtotal removal. This would amount to 48 to 72 Gm. Another yardstick would be the surgeon's own conception of how much of the pancreas was removed, estimating that removal of two-thirds to four-fifths of the organ would constitute subtotal removal.

If we consider Tables I and II tabulating 16 cases of partial resection of the pancreas where a tumor was found, it is evident that all of these patients had a very low fasting blood sugar and the symptoms of hypoglycemia were severe. The resection of the pancreas consisted in most part of removal of the tail of or the tail and part of the body of the pancreas. The amount of pancreatic tissue removed, when stated, was up to 23 Gm. The character of the tumor found in the resected tissue was islet adenoma, 11; carcinoma, 4; hamartoma, 1. There were 4 postoperative deaths. Eleven of the remaining patients remained symptom free of attacks of hypoglycemia for from four months to six years, 7 having been observed for more than two years. One patient had a recurrence of symptoms six months postoperatively.

In 2 patients where subtotal resection of the pancreas was carried out and the tumor was found in the resected portion, 1 patient died postoperatively but the other remained symptom free for ten months.

In 4 patients a subtotal resection of the pancreas was carried out and no tumor was found in the resected specimen. Subsequently a tumor was found and removed from the head of the pancreas.

Summarizing this group of 22 patients where a partial or subtotal pancreatectomy was carried out because of hypoglycemia and a tumor was found in the resected portion or at a subsequent operation, the results are simply those that one would expect following the successful removal of an islet tumor. This group also emphasizes the importance of careful exploration of all parts of the pancreas and the advisability of resection of the pancreas if no tumor can be found. If inadvertently the head of the pancreas were not explored and resection of the gland did not result in cure, a plain indication for another operation and exploration of the head of the pancreas is present.

Our interest in this study lies in the two groups of patients having partial or subtotal removal of the pancreas for spontaneous hypogly-

TABLE IV

PARTIAL RESECTION OF PANCREAS (NO TUMOR FOUND)

(FROM 8 TO 28 GM. OF PANCREAS REMOVED)

	NO. CASES	CURED	IMPROVED	NO IMPROVEMENT	DIED
Normal	15	2*	2	7	4
Hyperplasia	3†	1	1	1	
	18	3	3	8	4

*One patient was a 9-month-old baby.
†Nine and one-half grams of tail removed, question of tumor.
Received for publication, April 26, 1940.

cemia where no tumor was found in the resected portion of the pancreas and the pancreatic tissue removed was normal or showed a hyperplasia of the islet cells.

In Table IV where a partial resection of the pancreas was carried out in 18 patients and no tumor was found, there were 15 patients in whom the pancreas was normal histologically and 3 in whom hyperplasia of the islet cells was present. The minimum blood sugar in this group was below 50 mg. per cent in 14 patients. There was an operative mortality of 4 patients, or 22 per cent. Of the 14 survivors only 3 were free from attacks, 3 were moderately improved, and in 8 patients the attacks continued. Of these patients, 4 had 14 to 28 Gm. of pancreas removed, with some improvement in 1 and no abatement of symptoms in 3.

In Table V we have listed a group of 17 patients who have had a removal of from 35 to 60 Gm. of pancreas for spontaneous hypoglycemia. No tumor was found in the resected tissue in these patients. The examination of the pancreatic tissue revealed a normal pancreas

TABLE V

SUBTOTAL RESECTION OF PANCREAS

(FROM 35 GM. TO 90% OF PANCREAS REMOVED)

	NO. CASES	CURED	IMPROVED	NO IMPROVEMENT	DIED POST-OPERATIVELY
		No Tumor Found			
Pancreas normal	14	10	1	2	1
Hyperplasia of the islets	2	1		1	
Pancreatitis	1	11		1	
	17	11	1	4	1
		Tumor Found in Resected Area			
	2	2			
		No Tumor Found			
	4	3	1		
Total	23	16	2	4	1

TABLE VI

SUBTOTAL RESECTION OF PANCREAS

AUTHOR	PUBLICATION	AGE	DURATION SYMPTOMS	TYPE OF SYMPTOMS	MINIMUM BLOOD SUGAR	OPERATION	PATHOLOGY	RESULT
				No Tumor Found				
1. S. Harris (Taylor)	J. A. M. A. **100**: 321, 1933.	20	2 yr.	Narcolepsy	50	One-half body and tail	Normal pancreas	Well, 6 yr.
2. E. A. Graham and A. F. Hartman	Surg., Gynec., & Obst. **59**: 474, 1934.	1	9 mo.	Convulsions	6	80-90% resected	Normal pancreas	Symptom free 4 yr.; mentally deficient
3. S. Harris (Drennan)	South. Surg. **3**: 199, 1934.	32	?	Fainting	60	One-half body and tail	Normal pancreas	Symptom free 4 yr.
4. G. Thomason	West. J. Surg. **43**: 185-192, 1935.	43	3 yr.	Weakness, fatigue	40	Cautery removal close to head; spleen removed (50 Gm.)	Normal pancreas	Symptom free 4 yr.; normal blood sugar
5. W. F. Rienhoff, Jr., and Dean Lewis	Bull. Johns Hopkins Hosp. **54**: 386, 1934.	39	18 mo.	Unconsciousness	37	Resection tail and one-half body	Normal pancreas	Died first postoperative day
6. J. M. McCaughan and G. O. Broun (Case 3)	Ann. Surg. **105**: 354, 1937.	26	24 yr.	Convulsions	40	Subtotal resection 40.2 Gm.; about 80 per cent of the pancreas	Normal pancreas	Recurrent symptoms; low blood sugar
7. L. P. Engel	Personal communication to Whipple	55		Unconsciousness	Low	Subtotal resection	Normal pancreas	Symptom free 7 yr.

8. R. Woodyatt et al.				Convulsions	Low	Subtotal resection 48 Gm.; spleen also resected	Normal pancreas	Symptom free 2 yr.
9. S. Harris (Drennan)	South. Surg. 3: 199, 1934.	27	4 mo.	Convulsions	65	Excision one-half body, tail	Pancreatitis	Unimproved 4 yr.
10. H. E. Simon	South. Surg. 3: 199, 1934.	26	3½ mo.	Unconsciousness	51	Subtotal resection 60 Gm.	Hyperplasia of islets	Symptom free 3 yr.; died in motor accident
11. J. L. McCaughan and G. O. Broun (Case 6)	Ann. Surg. 105: 354, 1937.	24	20 yr.	Convulsions	70 Normal	35 Gm. 1 inch from duodenum	Normal with hyperplasia of islets	Recurrent symptoms
12. L. A. Womack and W. H. Cole	Ann. Surg. 105: 370, 1937.	36	4 yr.	Convulsions	60	Tail, ⅔ of body (40 Gm.)	Normal	Symptom free
13. L. A. Womack and W. H. Cole	Ann. Surg. 105: 354, 1937.	26	3 yr.			Tail, ⅔ of body (40 Gm.)	Normal	Improved; no return of convulsions
14. J. M. Clarke	Australian & New Zealand J. Surg. 8: 66-73, 1938.			Weakness, drowsiness	Low	35 Gm. removed; spleen also removed		Well except for spasm flexor muscle of arm
15. L. Engel	Personal communication.			Unconsciousness				Symptom free except low blood sugar
16. L. A. Womack	Personal communication.				45-55	Subtotal resection ¾ pancreas	Normal	Very little improvement

TABLE VI—CONT'D

AUTHOR	PUBLICATION	AGE	DURATION SYMPTOMS	TYPE OF SYMPTOMS	MINIMUM BLOOD SUGAR	OPERATION	PATHOLOGY	RESULT
17. W. C. Carrol	Minnesota Med. **20**: 229, 1937.	30	9 mo.	Unconsciousness	55	Resection 54 Gm.		Improved 1½ yr.; nervous depression
				Tumor Found in Resected Area				
1. O. Wangensteen (Case 2)	Minnesota Med. **18**: 265, 1935.	37		Convulsions	30	Subtotal resection ⅗ to ⅔	Adenocarcinoma	Symptom free 3 yr.; mental deterioration
2. L. P. Engle	Personal communication to Whipple	38		Unconsciousness	Low	Subtotal resection	Adenoma in tail	Symptom free 10 mo.
				No Tumor Found				
1. R. Graham	Personal communication to Whipple	27		Unconsciousness	26	(1) Subtotal resection; (2) subsequent removal adenoma in head	Adenoma	No change symptoms; improvement
2. 3. 4. A. Whipple	Chicago Surg. Soc. Dec., 1939.			Hypoglycemic attacks	Under 50	Subtotal resection subsequently finding tumor in head	Islet tumors	

in 14 patients, hyperplasia of the islet cells in 2, and a pancreatitis in 1 patient. Of these patients, 11 are relieved of the symptoms of hypoglycemia, 7 having been followed for over two years. There was only 1 operative death. Of the 4 unimproved patients, two had a fasting blood sugar of 65 to 70 mg. per cent before the operation and therefore may not strictly belong in the group giving the characteristic triad of symptoms.

There were 15 patients having a removal of 40 to 60 Gm. of pancreas where no tumor was found. Ten of these patients are apparently cured.

We have included in the group of patients cured of their attacks of hypoglycemia one patient who has subsequently shown evidence of mental deterioration (Graham's case), one patient who has had an occasional flexor spasm in one arm, and still another who has had two periods of nervous depression since the operation.

If we consider the mortality rate of the 23 patients who have had a resection of over 30 Gm. of pancreatic tissue, we find it to be 4.3 per cent. This low mortality rate compared to the 16 per cent mortality in removal of adenomas is probably a happenchance but still indicates that the operation is fairly safe.

This review of the results of partial and subtotal pancreatectomy was prompted by an experience in resection of 48 Gm. of pancreas in a patient with marked hypoglycemia where no tumor was found and the patient has remained well for nearly two years following the operation. Only a short case history will be given here as a more detailed description of the case will be given elsewhere by Rollin T. Woodyatt and Leo K. Campbell.

CASE REPORT

A male, 21 years of age, came to the Presbyterian Hospital on May 1, 1938, with no significant past history or dietary indiscretions, and developed in the course of a few days severe generalized tonic and clonic seizures with marked muscle irritability and local muscle spasm between the severe attacks. His laboratory findings were: serum Ca, 9.5; serum protein, 2; urea nitrogen, 12.7; uric acid, 3.8; creatinine, 1.3; total N.P.N., 33.3; CO_2 volume per cent, 48.7; chloride as NaCl, 479; Kahn, negative.

Glucose tolerance	Sugar 95
1 hour	Sugar 66
2 hours	Sugar 91
3 hours	Sugar 107
The urine sugars were	35.6 mg.
	49 mg.

The sella turcica was normal. Cortin was given in doses of 1 to 4 c.c. for five days without effect. When the patient came to the operating room, in spite of a previous injection of hypertonic glucose solution, he had a convulsion on the table so that more sugar was given and continued during the operation. The operation was carried out on May 27, 1938, under gas ether. A transverse upper abdominal incision was made. The gastrocolic omentum was divided. Careful examination

revealed no tumor in a rather small, pale pancreas. The adrenal glands were normal. Beginning at the tail, the pancreas was mobilized from below upward, but as the resection began it was found that the splenic vessels were imbedded in the superior surface of the pancreas so they were divided somewhat to the right of the median line. Forty-eight grams of pancreas were removed as well as a normal-appearing spleen. The pancreas was removed by sharp dissection, catching the vessels as they appeared. The cut surface of the pancreas was approximated with interrupted catgut stitches. A small nodule of pancreas was left in the curve of the duodenum. Two cigarette drains were left. Following the operation the patient was transfused. The day after operation the blood sugar was 280 mg. per cent and the urine showed sugar at seven drops. On June 14, 1938, the patient began to run a temperature which necessitated the opening of an abscess which was followed by a fistula which persisted about a month. The patient has been well since the operation, has had normal blood sugar and no muscular irritability.

CONCLUSIONS

In patients with the Whipple triad of symptoms and in whom extrapancreatic causes of hypoglycemia have been excluded as carefully as possible and dietary management has failed, exploration of the pancreas is indicated. A careful search for an islet tumor including mobilization of the duodenum and inspection of the head of the pancreas failing to demonstrate a tumor, a clear indication is present for subtotal resection of the tail and body of the pancreas up to the superior mesenteric vessels. This operation has been carried out in seventeen patients whose records have been found in the literature with favorable results and should be a part of the program in the treatment of spontaneous hypoglycemia until more knowledge of the underlying causes of the condition offers a better solution of the problem.

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THE PORTAL CIRCULATION AND RESTORATION OF THE LIVER AFTER PARTIAL REMOVAL

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THE practice of surgery has undergone many progressive changes during the period of years spanned by the length of life of the two surgeons to whose memory this volume is dedicated. Not the least important of these changes has been the increased application of knowledge obtained by experimental research to clinical surgery. There also has been an increase in the utilization of surgical procedures and methods in the experimental investigation of fundamental problems relating to the patient. This paper, dealing wholly with the results of experimental research and probably without clinical significance, is presented for publication in this special volume on the basis that it is representative of one phase of surgical progress, the application of surgical methods to the experimental investigation of fundamental processes.

Many surgical procedures must be considered carefully in relation to physiologic processes because such procedures cause the loss of all or a part of a functional activity or an organ for which physiologic compensation must be made. Fortunately in most instances the body possesses a functional reserve of many organs so that the remaining organ, in the case of paired organs, or the portion of an organ can readily compensate for the physiologic loss necessarily produced by such surgical procedures. Knowledge concerning the stimulus and mechanism causing physiologic compensation for the loss of a functional activity, organ, or portion of an organ is as yet in many instances incomplete. In view of the fact that often the feasibility of an operation or the beneficial effect expected from its use depends upon certain physiologic compensations occurring as a result of its performance, studies of the causal mechanism of such compensation may be of importance.

Compensatory hypertrophy, or restoration as we prefer to name the process, occurs to a remarkable degree in the liver following injury or partial removal and is in fact one of the most outstanding characteristics of hepatic tissue. The process is readily investigated by removal of various portions of the organ which is a feasible procedure to perform in many species of animals. The results of the early investigations on the subject have been reviewed by Rous and Larimore and by Fishback.[3] The data obtained by these early investigators supplemented by those of several more recent studies[1, 4] furnish a fairly complete history of the process of restoration of the liver after partial removal.

The restorative process appears to begin almost immediately after operation and is certainly initiated before the end of the first twenty-four hours. The rate of restoration varies, depending upon the species of animal used and the relative amount of liver tissue removed. The process occurs more rapidly and the total amount of liver tissue restored is greater when more than 50 per cent of the original liver mass is removed than when less than this amount is ablated, although it does occur even when less than 20 per cent of the hepatic tissue is removed. After the remaining liver tissue has been restored to a certain degree, no further increase occurs, even though the animal lives for many months after operation (Table I).

TABLE I

RESTORATION OF LIVER AFTER PARTIAL REMOVAL

NO.	BODY WEIGHT AT OPERATION (KG.)	BODY WEIGHT AT NECROPSY (KG.)	TIME BETWEEN OPERATION AND NECROPSY (DAYS)	ESTIMATED WEIGHT OF LIVER AT OPERATION (3.5% BODY WEIGHT) (GM.)	AMOUNT OF LIVER TISSUE REMOVED AT OPERATION (GM.)	ESTIMATED WEIGHT OF LIVER AT NECROPSY (3.5% BODY WEIGHT) (GM.)	WEIGHT OF LIVER TISSUE AT NECROPSY (GM.)
1	14.0	13.2	10	490	212	462	310
2	11.0	10.0	11	385	220	350	270
3	13.2	12.3	17	462	306	430	337
4	14.0	13.3	57	490	278	465	460
5	15.9	14.2	64	556	288	497	408
6	11.9	10.2	98	416	340	357	418
7	12.0	10.9	101	420	244	381	314
8	10.5	10.2	133	367	212	357	310
9	10.1	11.2	137	353	154	392	412
10	11.0	10.5	306	385	245	367	326
11	17.3	16.6	320	605	416	381	661
12	15.9	15.6	321	556	256	546	414
13	13.3	13.3	341	466	256	466	568
14	11.7	11.9	347	409	281	416	570
15	14.5	14.5	387	507	354	507	442

The gross appearance of the restored liver is very characteristic and can always be readily recognized. The edges of the lobes of the restored liver are rounded as compared to the knifelike edges of the lobes of the normal organ. The body of the lobe becomes dome-shaped and the lobe as a whole tends to become spherical. Sometimes there is a prolongation of one or more lobes. There is an increased friability of the hepatic tissue and the total mass of the restored liver may increase to an amount equal to or sometimes slightly greater than the amount of tissue removed at operation.

The microscopic changes in the restored hepatic tissue are not as definite or as easily recognized as the changes in gross appearance. Immediately after operation the hepatic cells appear swollen and many

remain larger than normal for several days. Mitotic figures begin to appear very soon after operation and are most abundant during the greatest period of hepatic tissue increment. The hepatic lobules are usually larger during the restorative process. It is usually impossible to differentiate restored liver tissue from normal hepatic tissue microscopically after the completion of restoration by any known method.

There is evidence that restored hepatic tissue is in certain respects not quite the same as normal liver tissue. The restored liver appears to react slightly differently in regard to physiologic stress and hepatic poisons. However, it has never been demonstrated that it has a reduced functional capacity.

The restoration of hepatic tissue after partial removal of the organ has been given the usual terms applied to this process when occurring in other organs as compensatory or work hypertrophy and is conceived as being due to a physiologic lack. But since the liver has many functions, a deficiency of hepatic tissue should produce a physiologic lack in regard to many physiologic processes. The stimulus for restoration could be owing to overwork in respect to one or several functions. If it were proved that overwork in regard to specific functions of the liver was responsible for the restoration of hepatic tissue after partial removal, efforts could be concentrated on the investigation of methods of quantitation of one or more such functions and thus afford the possibility of development of a real functional test for the liver.

The first evidence that the restoration of the liver after partial removal might not be a work hypertrophy and the stimulus causing it a functional lack came with the discovery of methods for decreasing the restoration or abolishing it altogether.

Rous and Larimore ligated the branches of the portal vein to the main liver of the rabbit, in which species the organ is almost completely separated into two unequal parts. The portion of liver deprived of portal blood underwent simple but complete atrophy while the hepatic tissue receiving all the portal blood hypertrophied to an amount equal to the original mass of liver tissue. They found that the atrophy of the lobes with ligated portal radicles was conditioned on hypertrophy of the remaining portion. The atrophy did not occur when the hypertrophy of the other portion was prevented by occlusion of the bile ducts draining it. The results of this investigation were important in giving direction to subsequent studies.

Mann and Magath, and later Mann, Fishback, Gay, and Green[8] removed various portions of the liver from dogs in which the portal blood had been diverted from the organ by making a stoma between the portal vein and vena cava with ligation of the former (Eck fistula) some weeks previous to the hepatectomy. They found that restoration was absent or occurred to only a slight extent in the atrophic liver deprived of portal blood. Mann and his co-workers[9] ligated the common bile duct and

found that, after the characteristic changes in the liver due to portal obstruction had occurred, the restoration of the liver after hepatectomy was greatly decreased. They[10] also found that restoration after partial removal was almost absent in the cirrhotic liver produced by the administration of carbon tetrachloride.

Stephenson[12] found that, when partial ligation of the portal vein was combined with partial removal of the liver in the rat, restoration was decreased. The amount of restoration appeared to be indirectly proportional to the amount of restriction of the portal vein.

Higgins, Mann, and Priestley[5] studied restoration of the liver after its partial removal in the chicken. In this species as in many other species there is a natural anastomotic channel between the portal and systemic systems. The liver is divided into two main lobes, the right and left. The left lobe, which is approximately one-third of the organ, can be easily removed. Following such removal, as a rule, little, if any, restoration occurred. The anastomotic channel was then ligated and several weeks subsequently the left lobe of liver was removed. Although restoration usually occurred following these procedures, it was not marked and it was never complete. The inferior vena cava was then ligated as far cephalad as possible. This forced much of the blood from the vena cava caudal to the point of ligation through the anastomotic channel into the portal system and thus increased the flow of blood through the liver. When the left lobe of liver was removed several weeks subsequent to these procedures, restoration of the liver always occurred, was usually complete, and was often greatly in excess of the tissue removed. Furthermore, ligation of the vena cava alone was often followed by increase in size of the liver.

In many respects a liver which has lost its portal blood supply presents an exactly opposite appearance to the liver from which a portion has been removed.[13] The hepatic tissue loses its turgidity and becomes flabby immediately after the diversion of the portal blood. The organ undergoes certain definite changes which give it a characteristic appearance. On gross examination, the most outstanding changes are in size and color. It atrophies to approximately one-half its normal size or less (Table II). Its shape and contour remain the same, but there is a decrease in all dimensions to about one-half the normal, and it becomes characteristically pale, mottled, and yellow. Microscopic changes are also definite. Atrophy of the central portions of all lobules occurs with accumulation of fat in the hepatic cells of these regions. Frequently the accumulation of fat in the hepatic cells is so great that only a rim of the protoplasm of the cell with a nucleus pushed to the periphery remains. After these changes, which occur initially in the central portion of the lobule, have extended to a considerable extent to the periportal regions, the atrophy becomes stationary and will remain thus for the remaining period of life. While Eck-fistula animals can rarely

TABLE II

ATROPHY OF LIVER AFTER DIVERTING PORTAL BLOOD (ECK FISTULA)

NO.	BODY WEIGHT AT OPERATION (KG.)	BODY WEIGHT AT NECROPSY (KG.)	TIME BETWEEN OPERATION AND NECROPSY (DAYS)	ESTIMATED WEIGHT OF LIVER AT OPERATION (3.5% BODY WEIGHT) (GM.)	ESTIMATED WEIGHT OF LIVER AT NECROPSY (3.5% BODY WEIGHT) (GM.)	WEIGHT OF LIVER TISSUE AT NECROPSY (GM.)
16	12.2	10.4	28	427	364	196
17	14.8	10.6	35	518	371	168
18	12.4	10.7	35	434	374	240
19	15.0	12.8	35	525	448	268
20	18.5	15.9	42	647	556	390
21	14.3	10.7	42	500	374	180
22	15.5	12.9	42	542	451	270
23	21.9	17.3	42	766	605	350
24	13.4	9.9	42	469	346	174
25	19.5	14.9	49	682	521	250
26	11.9	9.1	49	416	318	265
27	14.8	11.8	56	518	413	240
28	13.9	11.0	70	486	385	256
29	11.1	8.8	70	388	308	164
30	9.2	7.7	77	322	269	150
31	11.7	8.1	84	409	283	156
32	12.1	8.1	192	423	283	154
33	18.9	14.3	192	661	500	234

be maintained at their preoperative weight, the decrease in weight of the liver far exceeds the loss in body weight.

An analysis of the various methods discovered to date which will decrease or abolish the capacity of the liver for restoration reveals the fact that in each the flow of portal blood is either restricted or completely lacking. This fact suggests that the presence of the portal circulation may be as important in the causation of hepatic hypertrophy as its absence in producing hepatic atrophy. The contrast of the rapidity and amount of restoration in a normal liver with intact portal circulation after partial removal of the organ with the almost total lack of restoration in the liver without portal blood supply is both striking and significant.

The results of the investigations cited prove that restoration of liver tissue after partial removal to a significant amount depends upon an intact portal circulation, that injuries to the liver which restrict the portal circulation also cause a decrease in restoration, and that atrophy of the liver occurs in the absence of the portal blood flow. They do not indicate whether the stimulus causing the restoration is owing to the portal blood itself or the presence or absence of some of its constituents. Since diversion of the portal blood does not decrease the need of the organism for the performance of hepatic function, it would appear that,

if the stimulus for restoration were purely functional, a liver without portal blood would also be restored. Factors which might modify this assumption are the following: The portal blood comprises approximately two-thirds of the blood supply of the liver, so that in its absence there may not be sufficient blood for restoration. Since the circulation of the liver is unique in that it comes from two sources, one of which is venous in character and carries the absorption products from the intestinal tract as well as many substances elaborated by the organs draining into it, the possibility exists that the stimulus causing restoration is in a sufficiently high concentration to act only in the portal blood. It is also conceivable that failure of restoration to occur is owing to a loss of such a capacity in the hepatic cell since all procedures which decrease restoration also injure the hepatic cell.

In order to test all these assumptions it was essential that the portion of the liver left after partial removal should have its normal supply of portal blood, be normal hepatic tissue, and not be forced to afford passage to the portal blood normally passing through the liver tissue removed. The requirements for such a test were met in part by making in the mammal an open anastomotic channel between the portal and systemic venous systems, which as previously mentioned, occurs naturally in many species of the lower forms. To accomplish this a stoma was made between the portal vein and vena cava, without permanent ligation of either, thus permitting the blood to pass freely between the two vessels, depending upon the difference in pressure in them. Various portions of the liver were then removed. If the stimulus causing restoration is due to some substance or substances in the portal blood, restoration should occur because the remaining portion of the liver was left intact with its normal circulation. If the restoration is due to the portal blood which normally passed through the liver, tissue removed being forced through the remaining portion of the liver, restoration should not occur because this excess blood could pass directly through the stoma into the vena cava. An important source of error in the method is that owing to variations in size of the stoma in relation to diameter of the portal vein, more or less blood than passed through the liver tissue removed, might be shunted into the vena cava.

METHOD

Details of the method used to test the importance of the portal circulation for restoration of the normal liver after partial removal are as follows: All experiments were performed on dogs. All operative procedures were carried out under ether anesthesia and with surgical technique. A stoma was made between the portal vein and vena cava of the same type and employing the same technique as that used in making an Eck fistula. This technique has been described elsewhere

and need not be given in detail here.[2] Suffice it to state that the method of establishing a common opening between the two veins consists of the following steps:

1. The operative incision extends from the costal angle at the midline to the right flank. It begins at the costal angle and is a midline incision for about 8 cm. It then cuts obliquely across the right rectus muscle to the semilunar line, along which it extends caudally as far as necessary. This incision is very important as it is the only type of incision I have found which provides adequate exposure of the proper area of the two veins.

2. The duodenum is grasped firmly and pulled upward and to the left, care being taken to prevent making a rent in the delicate mesentery of the duodenum. All of the intestines found in the right upper quadrant are packed to the left of the duodenum and its mesentery.

3. A loose linen ligature is placed around the portal vein between the site of entrance of the pancreaticoduodenal vein and the liver.

4. The adventitia is removed from the right side and anterior surface of the portal vein for a distance extending caudally as far as possible from the entrance of the pancreaticoduodenal vein. The vena cava is left undisturbed.

5. A stay suture of two strands of fine silk is placed at each end of the exposed lengths of veins, holding them tightly together at each point.

6. A continuous suture, the posterior suture line, is now placed between the two stay sutures, using the needle of the caudal stay suture.

7. A cutting suture of heavy silk on a specially curved needle is placed as a mattress suture with an arm in each vein, the base slightly caudal to the cephalic stay suture and the free ends emerging from the veins just before reaching the caudal stay suture. The needle of the cutting suture is passed into the portal vein just cephalic to the caudal end of the previously placed suture line and parallel to it. It emerges from the portal vein just before reaching the cephalic stay suture and is passed into the vena cava in the opposite direction, emerging from this vessel at a point exactly opposite to its point of entrance into the portal vein.

8. An anterior row of continuous suture is now placed, beginning at the cephalic end. Care should be exercised to avoid including the cutting suture. Either needle of the stay sutures may be used to place this suture. The anterior suture ends with a mattress suture around the free end of the second stay suture and both ends of the cutting suture.

9. The free ends of the cutting suture are now grasped firmly and the enclosed walls of the two veins gently sawed through between the two rows of continuous sutures, care being taken to avoid sawing too long with one length of suture.

10. After the cutting suture has emerged intact, the free end of the second stay suture and the needle end of the anterior suture are tied together, closing the opening left by the removal of the cutting suture.

After completion of the stoma the temporary ligature was tightened to occlude the portal vein. It was not tied but held tightly with a serrefine in order to prevent injury to the vein. The purpose of the temporary occlusion of the portal vein was to determine whether the stoma between the two veins would permit passage of all the portal blood. The patency of the stoma was indicated if the color of the intestines did not change after the ligature was tightened. As will be noted later, this temporary ligature was also used as a part of the procedure to establish permanent patency of the stoma.

After it had been demonstrated that the stoma was functioning properly, various lobes of liver were ablated. The left lateral and left central lobes were removed together in the following manner: The left lateral lobe was delivered into the operative wound and the left coronary ligament severed. The pylorus and duodenum were then covered with a moist towel and grasped by the assistant who exerted gentle, even traction caudally and to the left. Both left lobes of liver were then lifted forcibly and a curved hemostat was clamped securely across the pedicle common to the two lobes as near the other portion of the organ as space would permit. A second clamp was applied just above the first clamp and parallel to it. A dry gauze pack was placed around the clamped pedicle between the hemostat and the remaining portion of the liver. Both lobes were grasped firmly to prevent oozing of blood and severed close to the upper clamp with a scalpel. A double linen ligature was tied firmly around the tissue crushed by each clamp, the lower ligature being placed first. The debris of liver tissue and blood around the ligated pedicle was carefully sponged away. In some experiments the right central or gall bladder lobe was also removed. The technique was essentially the same as for the left lobes, except even greater care was necessary to prevent injury of the blood vessels to the remaining lobes and the cystic duct was clamped before section.

The technique of removal of lobes of liver in the dog is not difficult, but fatal accidents may happen if the various steps of the procedure are not carefully performed. The more common causes of accidents are the following: (1) Injury to the blood supply to the remaining portion of the liver, particularly the small papillary projection of the caudate lobe. It requires only a few grams of liver tissue without blood supply in the peritoneal cavity to produce death. (2) Severance of the vessels of the ablated lobes by tightening the ligatures before they are released from the clamps. These vessels are very thin-walled and fragile and when stretched can be easily cut with a ligature. (3) Permitting liver tissue without blood supply to remain at the site of section. Even a

very small amount of such traumatized hepatic tissue is dangerous to life. All of these accidents can be avoided if recognized and adequate care is taken to avoid them.

While the effect of partial removal of liver on the remaining portion of the organ is well known, in order to have comparative specimens, in many instances carefully controlled experiments were done. Animals of approximately the same size and weight were used. All operative procedures were performed at the same operative period. The same number of lobes of liver were removed from each, but in one a stoma was made between the two veins previous to removal of the hepatic tissue.

All the animals were given the same postoperative care and diet which maintained them in good condition throughout the period of observations. The condition of the liver in regard to restoration was determined at various periods of time after operation. Observations of the organ were made either at an exploratory operation or at necropsy. Not only was the liver carefully observed and weighed at necropsy, but the stoma between the two veins was also examined to determine whether or not it had remained patent.

Both animals in the paired experiments, those in which the operations were performed during the same operative period and in which the same number of lobes of liver were removed from each animal but the stoma between the portal vein and vena cava made in only one animal, were weighed and killed at the same time by bleeding under ether anesthesia and observations made and data secured as in the other experiments.

RESULTS

At necropsy of the first group of animals used in preliminary experiments performed to test the validity of the method for exploration of the problem, the livers of the animals in which the stoma between the two veins had been made were identical with those in which only hepatectomy had been done. Approximately the same amount of restoration of liver tissue had occurred in each group of animals. Examination of the site of operation on the veins disclosed the fact that the stoma was not patent. Since the opening between the two veins consisted of a single longitudinal slit, a pressure differential had to be developed which would be adequate to force blood through the narrow stoma. Evidently the increase in pressure in the portal vein owing to the loss of the portal vascular radicles contained in the liver tissue removed had not been sufficient to force blood into the vena cava when the usual technique for making an Eck fistula had been employed. Without the passage of blood through the opening, the cut surfaces of the walls of veins were left in apposition and healed together.

Another series of operations were performed in which the operative technique differed from that used in the first group in two respects: (1) The stoma was made as long as the anatomy of the veins would

permit. The stoma thus extended from the hilum of the liver at the cephalic end to below the entrance of the renal vein into the vena cava at the caudal end. (2) The temporary ligature was kept securely tightened for several minutes after the lobes of liver were removed. Visual proof of patency of the stoma was obtained in several instances. In proper light the blood was seen through the thin wall of the portal vein flowing into the vena cava. The stoma was found to have remained patent in many of the animals in which this revised technique was used.

Fig. 1.—Specimens of liver obtained at operation and necropsy in a paired experiment. Animals were litter mates. Time between operation and necropsy was fifteen days. The date of operation and date of necropsy were the same for each animal. Specimen at top left weighed 387 Gm. and was obtained at necropsy from Animal 5a (Tables III and IV) from which the specimen at the bottom left, weighing 97 Gm., had been removed at operation. The specimen at the top right weighed 257 Gm. and was obtained at necropsy from Animal 5b (Tables III and IV) from which the specimen at the bottom right, weighing 123 Gm., had been removed and in addition a stoma was made between portal vein and vena cava. At necropsy the stoma was found to be patent but small. Note that restoration has occurred in each organ but is relatively slight in the presence of stoma.

Examination of the liver in the experiments in which the stoma remained patent revealed that the amount of restoration was less than in the control experiments. The remaining portion of the organ either had the same general appearance as it had at operation or showed relatively slight evidences of restoration. Its weight was but slightly greater than its estimated weight at operation (Tables III and IV, Fig. 1). The microscopic appearance of the hepatic tissue was normal.

The method for estimating the amount of liver tissue left after hepatectomy used in this investigation was the same as has been employed in

TABLE III

COMPARISON OF RESTORATION OF THE LIVER AFTER PARTIAL REMOVAL IN ANIMALS WITH UNDISTURBED PORTAL CIRCULATION (A) AND IN THOSE WITH PATENT STOMA BETWEEN PORTAL VEIN AND VENA CAVA (B)

NO.	BODY WEIGHT AT OPERATION (KG.)	BODY WEIGHT AT NECROPSY (KG.)	TIME BETWEEN OPERATION AND NECROPSY (DAYS)	ESTIMATED WEIGHT OF LIVER AT OPERATION (3.5% BODY WEIGHT) (GM.)	AMOUNT OF LIVER TISSUE REMOVED AT OPERATION (GM.)	ESTIMATED WEIGHT OF LIVER AT NECROPSY (3.5% BODY WEIGHT) (GM.)	WEIGHT OF LIVER TISSUE AT NECROPSY (GM.)
1a	10.9	13.2	46	381	133	462	383
1b	11.0	13.6	46	385	136	476	255
2a	12.9	12.3	40	451	274	430	373
2b	13.2	12.8	40	462	294	448	221
3a	15.3	16.2	20	535	277	567	610
3b	15.4	16.0	20	539	274	560	323
4a	15.6	16.4	25	546	270	574	558
4b	15.5	16.2	25	542	280	567	311
5a	8.0	9.0	15	280	97	315	387
5b	9.4	10.4	15	329	123	364	257

this laboratory for many years. It is admittedly only a rough approximation, but it is the best so far devised for the dog. Owing to the differences in the many breeds of dogs which reach the laboratory, this species cannot as yet be standardized as has been done with the rat. The method is based on a body weight-liver weight ratio and on the percental amount of liver tissue comprised in the various lobes as compared to the whole organ. McMaster and Rous found the liver weight to be 3.5 per cent of the body weight in dogs. In two series of our laboratory animals, each series consisting of 100 animals dying from causes not affecting the liver, the organ was found to comprise 3.45 per cent of the body weight. On the basis of these data the ratio of McMaster and Rous is used. The method of estimation based upon the

TABLE IV

DATA OBTAINED IN A PAIRED EXPERIMENT IN WHICH ANIMALS WERE LITTER MATES*

	ANIMAL 5A	ANIMAL 5B
Body weight at operation	8 kg.	9.4 kg.
Estimated weight of liver at operation	280 Gm.	329 Gm.
Weight of liver tissue removed*	97 Gm.	123 Gm.
Weight of liver remaining	183 Gm.	206 Gm.
Body weight at necropsy	9 kg.	10.4 kg.
Estimated weight of liver at necropsy	315 Gm.	364 Gm.
Weight of liver at necropsy	387 Gm.	257 Gm.
Total weight of liver (amount removed added to amount obtained at necropsy)	484 Gm.	380 Gm.
Weight of new liver tissue formed	204 Gm.	51 Gm.

*Hepatectomy only was done in Animal 5a; in Animal 5b a stoma was made in addition to partial removal of liver. Note that, while some of the figures are based on estimations, the total weight of liver (amount removed added to amount obtained at necropsy) is real and the difference found conclusive.

ratio of the weight of the various lobes to the total weight of the liver is even more unsatisfactory than the body weight-liver weight method. However, the left lateral and left central lobes of liver, those usually removed, are together approximately one-third of the organ and, with the addition of the right central lobe, more than one-half the liver.

COMMENT

The results of these experiments would appear not only to prove the conclusion reached in previous investigations that restoration of the liver after partial removal depends to a very great extent on the flow of portal blood through the organ, but also to suggest that the primary stimulus is the portal blood itself. While it would seem highly probable that, in the case of an organ with so many functions as the liver, there would be many stimuli, which, owing to a physiologic need, could cause restoration of hepatic tissue when it had been decreased below normal, the effect of such stimuli appears to be relatively slight compared to that caused by the stimulus of the portal blood flow and is secondary to the latter. While the restored liver tissue does actually compensate for a physiologic loss, its occurrence is apparently to establish an adequate portal pathway. The necessity for restoration of vascular channels appears greater than for the restoration of functionating hepatic tissue. It is quite possible that the stimulus and mechanism for the development of portal pathways through the remaining portion of the liver after partial removal, giving origin to restoration of the organ, are the same as those causing the formation of new areas of vascularization elsewhere in the body and the fact that the matrix happens to be hepatic tissue may be only a fortuitous circumstance. In this connection it should be noted that the control of the portal blood flow resides to a slight extent only in the liver but for the most part is located in the vasomotor controlled areas of the gastrointestinal tract and the other organs draining into the portal system. The liver has very little to say in regard to the amount of blood that passes through its portal channels.

The role of the portal circulation in the restoration of liver tissue after injury is not as definitely established as after partial removal of the organ. The procedure of removal of lobes of liver surgically is very simple compared to the destruction of liver tissue by hepatic poisons and infection. In the case of hepatic injury, other factors are operative in addition to the simple restoration of portal pathways and functionating hepatic tissue. The more important of these additional factors are the exciting agent which caused the injury and the processes of healing of the resulting lesion. In this complicated condition of the liver where physiologic and pathologic processes are occurring concomitantly, the significance of the flow of portal blood cannot be clearly discerned, but its importance cannot be doubted. Sufficient data are at hand to justify certain postulations. It appears highly probable that

restoration of hepatic tissue due to any particular agent continues, although possibly more or less imperfectly, until the portal pathways are partially occluded. Since the injury to liver tissue usually occurs in localized areas, the restoration is also localized. Each time a given hepatic area suffers injury, the vascular pathways are not completely repaired. Greater restoration occurs in those areas in which the hepatic cells and especially the vascular channels are least injured, giving rise to circumscribed masses of newly formed hepatic tissue. Finally, after repeated episodes of injury, the portal pathways become definitely restricted, greatly limiting or abolishing restoration. At this point the atrophic processes supervene.

Regardless of the cause and mechanism of restoration of liver substance, its occurrence is of great importance physiologically because there is thus assured a constant renewal of this vital tissue as long as the capacity for restoration persists. It is equally important pathologically. This remarkable characteristic of liver tissue must always be considered if the varying patterns of hepatic pathology are to be understood.

SUMMARY

The partial removal of the liver from a normal dog is followed by complete restoration of hepatic tissue within a fairly definite period of time. If a stoma is made between the portal vein and vena cava leaving both channels patent, thus permitting blood to interchange between the veins, at the same time the hepatic tissue is removed, restoration of the remaining portion of the organ is greatly decreased. The results of these experiments emphasize the importance of the portal circulation per se for restoration of the liver after partial removal. While there is evidence that stimuli other than the portal blood are operative in causing restoration of the liver, it has not been possible to determine the nature of such stimuli or to separate their action from that of the portal blood.

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WITH HOW LITTLE LUNG TISSUE IS LIFE COMPATIBLE?

Report of a Patient From Whom All Pulmonary Tissue Except the Two Upper Lobes Was Successfully Removed

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THE rapid development of thoracic surgery in recent years has made the extensive removal of pulmonary tissue technically feasible. The removal of a single lobe for bronchiectasis is now not only a common operation in the large thoracic clinics but it has also been made a relatively safe procedure with a mortality of 5 per cent or less. Even successful removals of a whole lung are now not unusual. Likewise, the removal of both lower lobes in cases of bilateral bronchiectasis has been performed on numerous occasions since Eloesser's[1] first case. Overholt[4] in 1937 reported the removal of both lower lobes and the right middle lobe in four stages from a girl 19 years of age. Eight months after the operation the vital capacity was 1,162 c.c.

The case about to be described represents a still more radical removal of pulmonary tissue in that not only were the two lower and the right middle lobes removed but also the lingula of the left upper lobe. It is now generally accepted that the lingula is the homologue of the right middle lobe and that because of the anatomical distribution of the bronchus and blood vessels it should be regarded as essentially a separate lobe. From a practical standpoint, therefore, this case represents the removal of four of the six lobes, and, as judged by reports in the literature, it is the most extreme example of successful radical removal of pulmonary tissue. Although only two months have elapsed since the completion of the second operation, the boy is able to walk rapidly for short distances without dyspnea, and his vital capacity is 1,200 c.c. It is to be expected that his improvement will continue and that his vital capacity will increase.

Heuer and Andrus[3] state that in their experiments dogs were able to live indefinitely after the removal of all of the left lung and of the middle lobe of the right lung, with two lobes, therefore, remaining. In 1933, Heuer,[2] in reviewing his previous experimental work with Dunn, Andrus, Rienhoff, Cave, and other associates, stated, however, that he had found that in the dog life and good health were compatible with only one remaining lobe. In those experiments it was found that the pleural space created by the extensive removal of pulmonary tissue was obliterated very quickly (usually in about two weeks), chiefly by a

marked hypertrophy of the remaining portion of lung. The dog is admirably adapted for such a mechanism because of the extreme mobility of its mediastinal partition.

It has been uncertain how much one could apply to the human being the findings obtained on dogs. The human case to be described, however, may be regarded perhaps as a counterpart of Heuer's dog experiments in which only two lobes were allowed to remain, since the dog has six lobes of pulmonary tissue. The removal of four of the lobes, therefore, is practically equivalent to the removal in the human being of the two lower lobes, the right middle lobe, and the lingula of the left upper lobe.

Theoretically, since the tidal air requirement (500 c.c.) of an adult of average size is only about one-eighth of his vital capacity, it might be assumed that the surgical removal of about six- or seven-eighths of the total volume of the lung would be compatible with life. This might be the case if it were never necessary to use more air than ordinary tidal air requirements. It happens, however, that at times of active exercise and in periods of stress of various kinds more than the normal amount of tidal air is used. Dyspnea, therefore, would frequently be present if the individual were left with only about one-quarter or one-eighth of his normal pulmonary tissue. Fortunately the compensatory mechanism of hypertrophy of the remaining lung tissue occurs to relieve the situation. Actually, in the case here described, although four of the six lobes were removed, it would be unjustifiable to conclude that the patient was suddenly deprived of two-thirds of his pulmonary tissue. The long-standing disease had resulted in a shrinkage of those lobes which were removed so that there had been an opportunity for the two upper lobes to become hypertrophied. Moreover, more than a year elapsed between the removal of the lung tissue on the right side and that on the left, another factor inducing the hypertrophy of the right upper lobe.

An abstract of the case follows:

CASE REPORT.—This boy, aged 14 years, was first admitted to the St. Louis Children's Hospital on Oct. 10, 1938. The chief complaint was persistent cough with large amounts of purulent sputum. The parents stated that the present illness began with an attack of pneumonia at 2½ years of age. This was complicated by an empyema on the right side and a drainage tube was inserted after the removal of a portion of a rib. The drainage was maintained for about two months. Subsequently the empyema cavity and the thoracostomy incision healed satisfactorily. From then on the boy has never been well. Frequent attacks of so-called pneumonia occurred and at all times the productive cough continued. Sometimes he has coughed up small amounts of blood but he has never had a large hemorrhage. During the past two years he has been in somewhat better health except for the persistence of the cough and sputum. His physical condition, however, has prevented him from going to school as much as he should have. Three years ago he was in bed for two or three weeks with acute mastoiditis. About three weeks ago he

was sent to a tuberculosis sanatorium because his physician thought he might have tuberculosis. At the sanatorium, however, his condition was diagnosed as nontuberculous bronchiectasis.

Examination disclosed a slight discharge from the right ear and rather marked clubbing of the fingers. There was a moderate secondary anemia and a total leucocyte count of 15,500. Bronchograms showed the terminal divisions of the

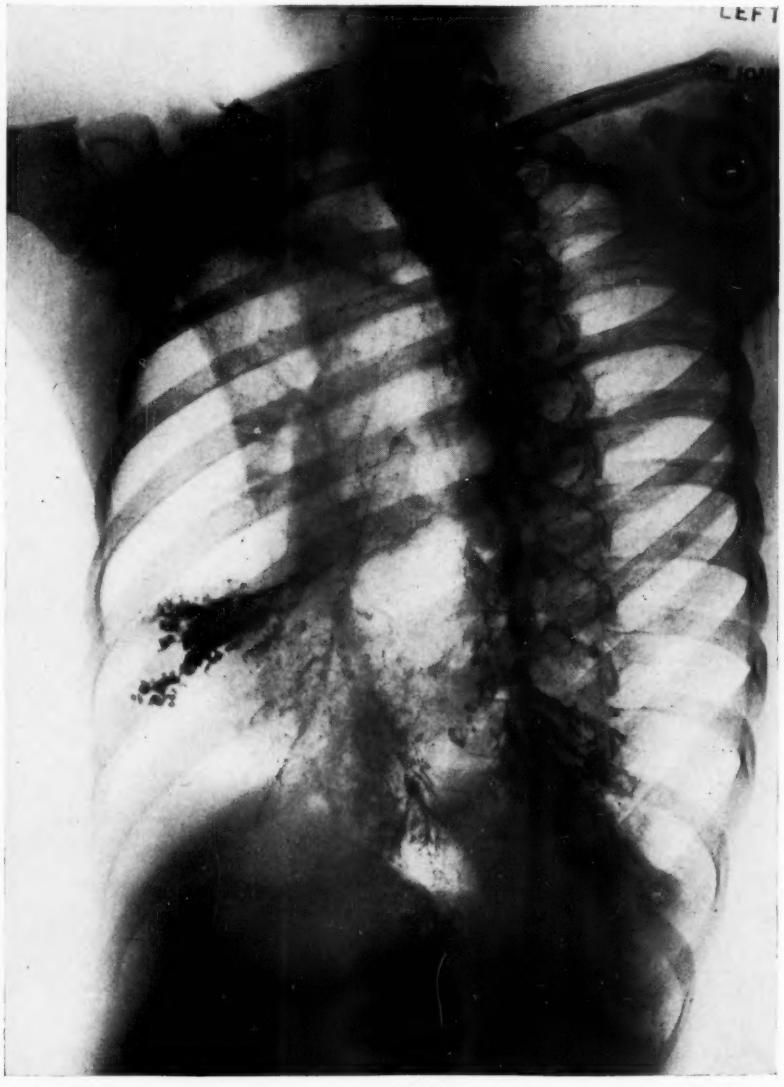

Fig. 1.—Bronchogram showing bronchiectasis of right middle and lower lobes. The lipiodol filling of the lower part of the lower lobe is concealed somewhat in the print by the shadow of the diaphragm.

left lower lobe bronchi to be dilated and clubbed. The lingular division of the left upper lobe bronchus also showed bronchial dilatation. Similar changes were noted in the middle lobe bronchi of the right lung and there was an irregularity in the lumina of the right lower lobe bronchi. On the basis of the bronchograms an x-ray diagnosis was made of bronchiectasis involving the left lower lobe and the lingula of the left upper lobe, the right middle and the right lower lobes.

A bronchoscopic examination by A. Stutsman revealed as its only significant feature large amounts of pus coming from the lobes noted as diseased in the bronchograms.

It was decided to attempt to remove all of the diseased tissue. The decision to begin on the right side was arrived at because, in view of the fact that the empyema had been on that side, it seemed probable that the most active disease would be there.

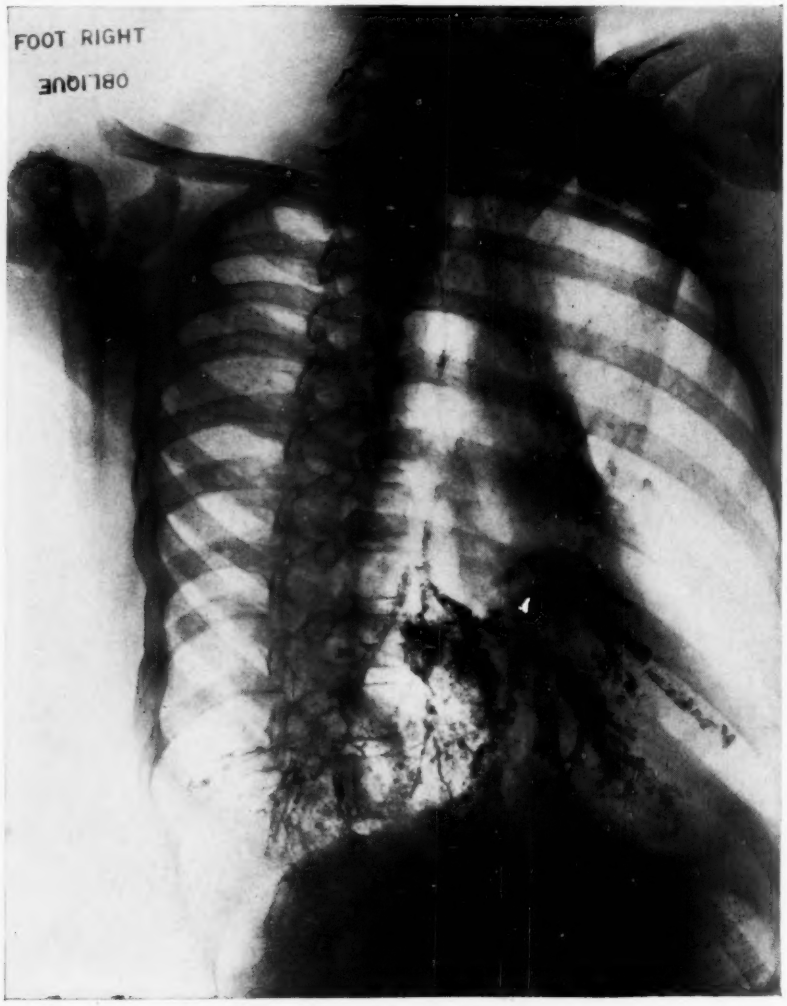

Fig. 2.—Bronchogram showing bronchiectasis of left lower lobe and of lingula of upper lobe.

The first operation was performed on Nov. 3, 1938. With intratracheal anesthesia with cyclopropane an incision was made beginning close to the spine at the level of the sixth dorsal vertebra which was brought down to the level of the seventh intercostal space and carried forward to about the anterior axillary line. The seventh and eighth ribs were found to be fused together as a result of the old empyema operation and it was necessary to resect both of them in order to enter the pleural cavity. The lung was firmly adherent to the chest wall by dense adhesions which required sharp dissection in order to mobilize the lower and middle lobes. The middle lobe was atelectatic and firmly adherent to the

mediastinal pleura. The interlobar fissure between the middle and upper lobes was incomplete and in order to free the middle lobe it was necessary to resect it from the upper lobe. Because the patient's condition was not entirely satisfactory it seemed advisable to complete the operation quickly and consequently a tourniquet was placed around the hilus of both the middle and lower lobes and the lobes were cut away. The stump was transfixed with No. 1 forty-day catgut and a mass ligation was made. Through stab wounds two rubber catheters were inserted through the seventh interspace into the thoracic cavity, one in approximately the midaxillary line, the other posteriorly in a line corresponding to the angles of the ribs. The wound was then closed in layers using pericostal sutures of No. 1 forty-day catgut to approximate the ribs as well as possible.

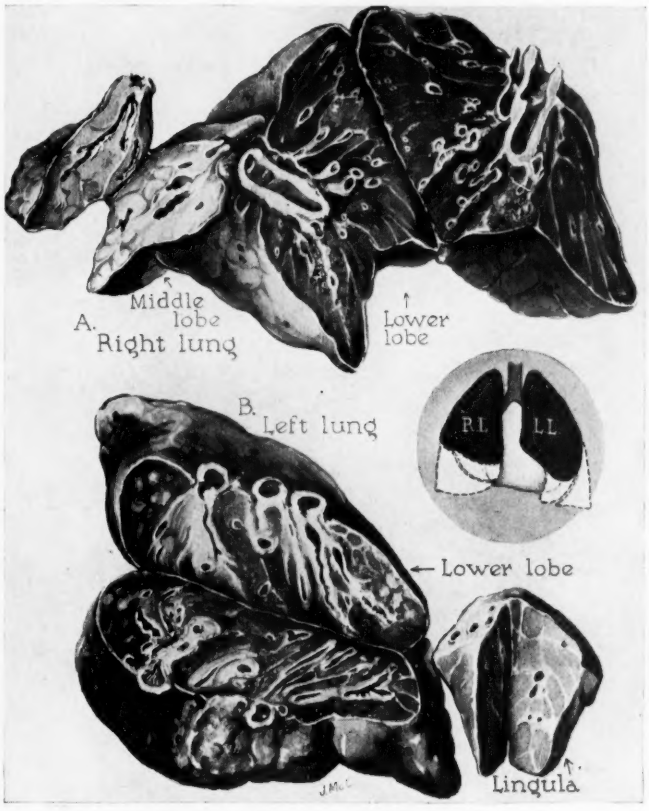

Fig. 3.—Drawing of removed portions of lungs after being cut open.

The skin was closed with a continuous dermal suture. When the operation was about two-thirds completed, the patient became cyanotic and his respiratory exchange was poor. Suction through the intratracheal catheter did not relieve the condition satisfactorily. Consequently, a bronchoscope was hastily passed by Dr. Stutsman and about 15 c.c. of thick purulent material tinged with blood was removed from the left main bronchus. A curved suction tip was then inserted into the various divisions of the bronchial tree which was well cleaned out. A marked improvement in the patient's condition was immediately noticed. After the completion of the operation another bronchoscopic aspiration was made before the patient left the operating room. He had also had a bronchoscopic aspiration in the operating room immediately before the operation was started. He, therefore, had three bronchoscopic aspirations in connection with the operation, one

immediately before, one during the course of the operation, and a third one immediately after the completion of the operation. It is probable that these were lifesaving measures. He developed a bronchial fistula and an empyema on the tenth postoperative day. He was discharged on Dec. 22 with the empyema cavity obliterated and the wound healed. He was still expectorating purulent sputum, but the amount was reduced about 50 per cent.

On Feb. 28, 1940, he was admitted to Barnes Hospital, rather than to the Children's Hospital, because he was then 15 years old. The interim history showed that since his operation he has been feeling much better. He states that

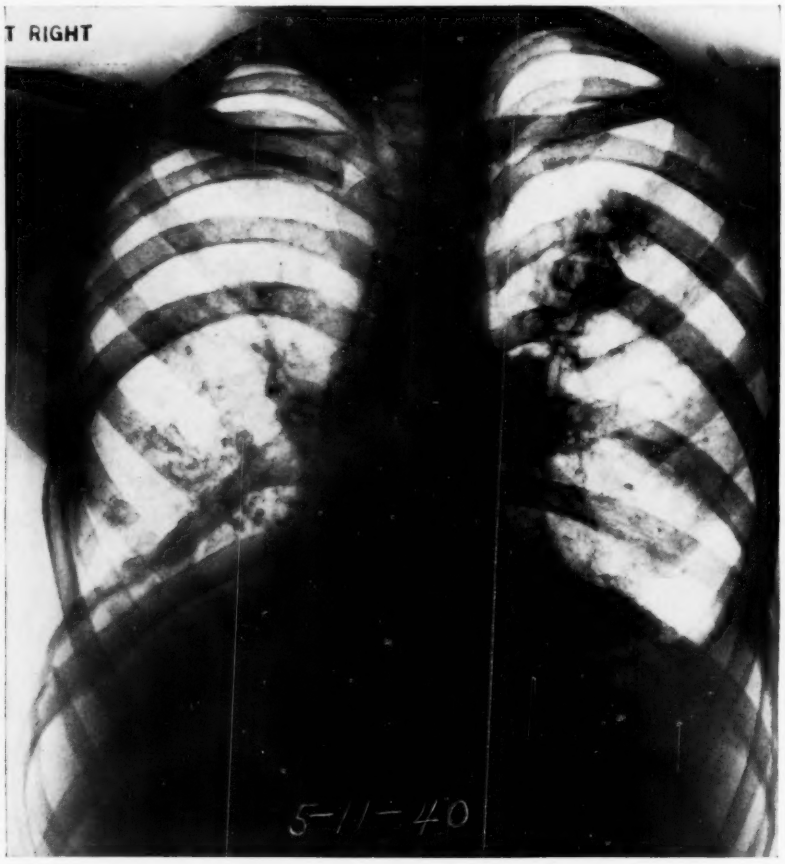

Fig. 4.—X-ray film at time of discharge after last operation.

he coughs only in the mornings and in the evenings. He was able to be in school continuously during the fall and winter of 1939. The right thoracotomy wound is solidly healed and gives no difficulty of any kind. A bronchoscopic examination by E. Kent on Feb. 29 showed a large amount of purulent secretion coming from the left lower lobe. A good view of the stump of the middle and lower lobe bronchus on the right side was available. The mucosa on the blind end was slightly hyperemic, but no other change was noted. On March 6 his second operation was performed. A bronchoscopic aspiration by Brian Blades was performed immediately before the operation was begun. Again under intratracheal anesthesia with cyclopropane an incision was made on the left side beginning at the level of the sixth rib close to its vertebral attachment and extending anteriorly over the level of the seventh and then the eighth rib to the anterior

axillary line. The sixth, seventh, and eighth ribs were divided close to their corresponding vertebrae and the pleura was entered in the seventh interspace. A partially atelectatic left lower lobe was found together with atelectasis of the lingula of the left upper lobe. A good many troublesome adhesions were found between the lower lobe and the diaphragm as well as between the lower lobe and the chest wall. Most of these required cutting between clamps. The inferior pulmonary ligament was followed to the root of the lower lobe. The interlobar fissure was also developed by blunt dissection to the root of the lower lobe. Individual ligation of the hilar structures was planned but abandoned for the tourniquet because of repeated respiratory difficulties which necessitated on several occasions the removal of the rib spreader and temporary closure of the chest wall. A tourniquet, therefore, was placed around the hilus of the lower lobe and a second tourniquet was placed about 3 cm. distal to the first. Amputation of the lower lobe was performed between them. A transfixion ligature of doubled No. 1 forty-day

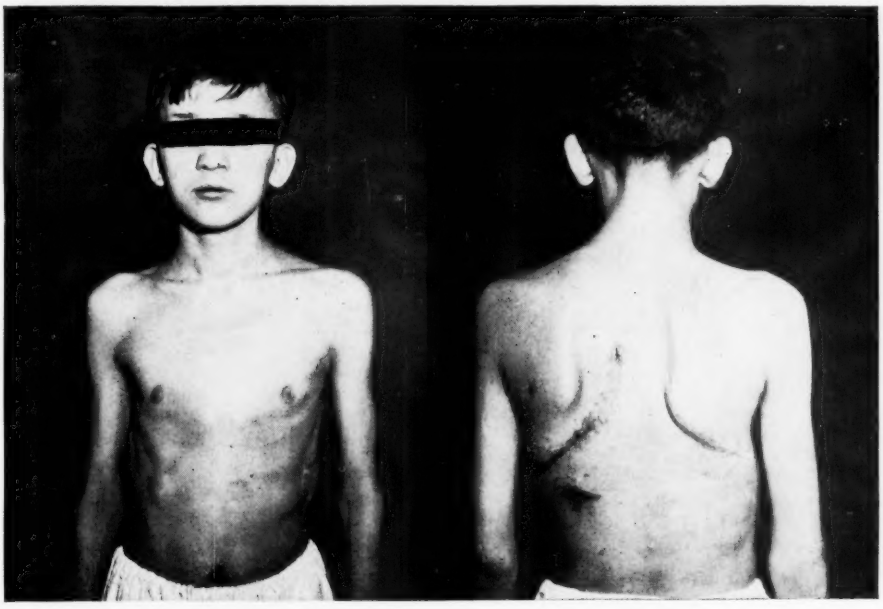

Fig. 5. Fig. 6.

Fig. 5.—Patient at discharge after last operation.

Fig. 6.—View of back at discharge after last operation. Wounds solidly healed. Irritation of skin from adhesive plaster on left side gives erroneous impression of unhealed wounds.

chromic catgut was placed around the stump of the lower lobe which completely prevented any hemorrhage. It was also noted that the bronchus was tightly closed. Several reinforcing interrupted sutures of No. 1 twenty-day chromic catgut were placed through the open surface of the amputated hilus. The lingula was resected between clamps and the wound in the upper lobe repaired by the use of a continuous invaginating suture. Catheters were inserted through stab wounds in the anterior and the posterior axillary lines. The chest wall was closed by approximating the ribs with pericostal sutures of catgut and by bringing the severed ends of the ribs together with twenty-day catgut placed through drill holes. A flap of the longissimus dorsi muscle was brought over the posterior angle of the incision and retained with interrupted sutures of catgut. The soft tissues were closed in layers and the skin sutured with dermal. The patient had

another bronchoscopic aspiration by Dr. Blades immediately after the completion of the operation. He was also given a transfusion of 500 c.c. of blood although there had been no hemorrhage.

Evidence of an empyema appeared on the fourth postoperative day and a bronchial fistula was demonstrable on about the eighth day after the operation. On March 29 the diagnosis of a pericardial effusion was made both by fluoroscopy and kymography. The patient also at that time was very dyspneic. Aspiration at the right of the sternum in the fourth intercostal space yielded only 20 c.c. of bloody fluid which was sterile on culture. From then on his convalescence was uneventful and he was discharged from the hospital on May 11 with his wound solidly healed, the empyema cavity obliterated, no cough or sputum, no dyspnea on ordinary exertion, and a vital capacity of 1,200 c.c. For the first time in his memory he has been free from cough and sputum. The clubbing of the fingers has disappeared completely.

SUMMARY

A case is reported in which the two lower lobes, the right middle lobe, and the lingula of the left upper lobe were removed because of bronchiectasis. Its interest and importance lie in the fact that it demonstrates that a comfortable existence is compatible with only the right upper lobe and the left upper lobe without the lingula. It apparently represents the most extensive removal of pulmonary tissue so far reported in the human being. It is, therefore, a link in the chain of information gradually being accumulated which will enable us to tell how much lung tissue can be removed safely.

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STUDIES ON THE EFFECTS OF THE INHALATION OF A HIGH CONCENTRATION OF OXYGEN IN EXPERIMENTAL SHOCK*

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THE fundamental pathologic change in shock consists of a discrepancy between the volume of blood in circulation and the capacity of the vascular bed, due to an increase in the capacity of the vascular bed or to a decrease in the volume of blood or to both. Regardless of the mechanism of the production of peripheral circulatory failure, a prolonged diminution in the effective blood volume results in tissue anoxia which is essentially that of the stagnant type. Most attempts at therapy have consisted of attempts to correct the disparity between the capacity of the vascular bed and the effective blood volume. Recently, attention has been directed again by Boothby, Mayo, and Lovelace[1] to the factor of anoxia in shock, and they have advised the inspiration of very high concentrations of oxygen in its treatment, especially during the early stages. Thus, they[1] administer pure oxygen routinely after major operative procedures, augmenting this with transfusions of blood when necessary.

The benefits to be obtained by the administration of a high concentration of oxygen have been outlined by Boothby and associates.[1] Thus, in the case of a retarded peripheral capillary circulation with the blood giving up as much as 80 per cent of its oxygen to the tissues, the capillary partial pressure of oxygen would fall from a normal of about 35 mm. to 14 mm. Hg. In this case the inspiration of 100 per cent oxygen, on the basis of the characteristic dissociation of oxyhemoglobin, could be expected to increase the amount of oxygen available to the tissues by as much as 50 per cent.

Our study was undertaken to determine, experimentally, the effects of the inspiration of these high concentrations of oxygen on moderate degrees of shock as produced by hemorrhage, histamine, and trauma.

METHODS

Dogs were used in all experiments. At a preliminary operation preparations were made for withdrawal of blood from sites which could not otherwise be readily approached. For this purpose an instrument[2] designed to permit withdrawal of portal venous blood without surgical exposure was inserted, and in addition the left kidney was explanted by the technique of Rhoads.[3]

*Aided by a grant from the Division of Medical Sciences of the Rockefeller Foundation.

Morphine sulphate, 0.001 to 0.0015 Gm. per kilogram of body weight was administered at the beginning of all experiments. Approximately one and one-half to two hours later, under procaine infiltration anesthesia, the left common carotid artery was cannulated and connected to a mercury manometer, a maximum-minimum valve being used. Respirations were recorded by the tambour method. Hematocrit readings were made in duplicate with Van Allen tubes.

Shock was produced in the following manner. In the case of *hemorrhage* blood was removed in small amounts at frequent intervals until a quantity equal to about 2 per cent of the body weight had been withdrawn over a period of approximately two hours. This resulted in an acceleration of pulse rate, decrease in pulse pressure, and a slight decline in the systolic pressure. In the case of *histamine* the drug was administered subcutaneously in repeated small doses of from 1 to 4 mg. until the systolic pressure was fairly stationary at approximately 100 mm. Hg. The average total dosage was 6 mg. administered over a period of approximately two hours. *Traumatic shock* was produced by repeated blows with a hammer to the soft tissues of a hind limb, avoiding the region of the main vessels and nerves. Generel anesthesia was induced by ether during the period of actual trauma which usually lasted from two to five minutes. A systolic blood pressure of approximately 100 mm. Hg was reached in from one to four and one-half hours following traumatization, with the average elapsed time being approximately two hours.

The right external jugular vein, the explanted renal vein, and the femoral vessels of one leg were exposed under local anesthesia to facilitate withdrawal of blood samples. After the desired alteration in the circulation had been induced, blood samples for gas analysis were drawn anaerobically and without stasis from the portal vein, the renal vein, the femoral vein, the femoral artery, and the right heart in that order and as rapidly as possible. Blood from the right heart was obtained by means of a short cannula introduced through the right external jugular vein. Immediately following the taking of samples, a quantity of citrated blood equal to that which had been removed was introduced into the femoral vein. Oxygen was then administered by means of a Benedict spirometer containing the pure gas. Inhalation was continued for approximately fifteen minutes and shortly before the end of this period another set of blood samples was obtained. The blood gas analyses were performed with the Van Slyke-Neill manometric apparatus.

In a few instances whole blood pH determinations were made with the Coleman pH electrometer. In addition a few determinations of cardiac output were made by use of the Fick principle.

RESULTS

Experiments were performed on twenty-three dogs and the results of these are presented in Tables I, II, and III. In general, the most consistent results were obtained in those experiments in which shock was produced by hemorrhage. This is probably due to the fact that the degree of shock could be more easily controlled and that there were less marked fluctuations in the blood pressures of these animals.

Hemorrhage.—There were five experiments of this type. At the time of withdrawal of the first blood samples for gas analysis, there was an average depression of 45 mm. Hg in the systolic and 6 mm. Hg in the diastolic pressures. The average increase in pulse rate was 89 per minute. Following the administration of pure oxygen, the systolic arterial pressure rose an average of 6 mm. Hg and the diastolic pressures were usually unchanged. The average pulse rate decreased slightly and the respiratory rate usually remained the same.

During the administration of oxygen, the oxygen capacity decreased slightly in three experiments and increased slightly in two, the average being a slight decrease. Arterial oxygen contents were increased in all instances. The oxygen content of blood from the femoral vein was lower than that from other vessels in all experiments. It increased appreciably following the administration of pure oxygen in four experiments and decreased slightly in one. All renal and portal venous oxygen contents were increased by the inhalation of oxygen. The average oxygen content of mixed venous blood from the right heart also was increased. The average increase in oxygen content with oxygen inhalation was greatest in the blood from the portal vein. The order of increase in O_2 content of blood from other localities was, from greatest to smallest, the femoral vein, the renal vein, femoral artery, and the right heart. The average results of these experiments are presented in Table I.

Histamine.—There were seven experiments of this type. The average decline in blood pressure following the injection of histamine hydrochloride was 65 mm. Hg systolic and 22 mm. Hg diastolic. The average increase in pulse rate was 122 per minute. After breathing pure oxygen for a period of approximately fifteen minutes, the systolic pressure had risen an average of 7 mm. Hg and the diastolic pressure had risen an average of 9 mm. Hg. The pulse rate usually became slower and the respiratory rate remained approximately the same.

The average of oxygen capacities was slightly below that of the samples drawn just before administration of oxygen. The oxygen content of blood from the femoral artery rose in all instances; whereas, that of the femoral vein rose in six instances and fell in one, the average being an appreciable increase. The oxygen content of samples from the renal vein showed an increase in five experiments and a decrease in one (only six samples were obtained); whereas, the content

TABLE I

THE EFFECT OF THE ADMINISTRATION OF PURE OXYGEN ON SHOCK PRODUCED BY HEMORRHAGE (AVERAGES OF THE RESULTS OBTAINED IN 5 EXPERIMENTS)

	B.P. IN MM. HG.	PULSE RATE PER MIN.	RESPIRATIONS PER MIN.	HEMATOCRIT VOLUME %	O_2 CAPACITY VOLUME %	CO_2 AND O_2 CONTENT, VOLUMES PER CENT									
						FEMORAL ARTERY		FEMORAL VEIN		RENAL VEIN		PORTAL VEIN		RIGHT HEART	
						CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2
Controls	170/99	76	51	43.8											
118 min. after first bleeding; total blood removed equal to 1.65 per cent body weight	125/93	165	17	46.6	23.78	32.60	20.75	45.87	7.64	35.35	18.18	39.70	12.52	40.65	11.03
After 15 min. of inspiring pure O_2	131/94	150	18		24.15	35.84	22.01	47.34	9.84	41.96	20.18	40.52	15.21	44.10	12.21
Average change resulting from the inhalation of O_2	+6/+1	-15	+1		+0.37	+3.24	+1.26	+1.47	+2.20	+6.61	+2.00	+0.82	+2.69	+3.45	+1.18

of portal venous blood was increased in four and decreased in three experiments. Blood from the right heart was increased in oxygen content in five instances and decreased in two. There was a definite increase in the average content of the renal, portal, and right heart blood, but this increase was not as marked as in experiments dealing with hemorrhage. In addition, the individual increases in venous oxygen contents were much more variable. The order of increase in oxygen contents was from greatest to smallest, femoral vein, renal vein, right heart, portal vein, femoral artery. This is in interesting contrast to the results obtained in the experiments on the effects of hemorrhage. The average results of these experiments are given in Table II.

Trauma.—There were eleven experiments of this type. Trauma to one of the posterior extremities resulted in an average reduction of 67 mm. Hg in the systolic and of 19 mm. in the diastolic pressures. The pulse increased an average of 148 per minute. Administration of pure oxygen resulted in practically no change in blood pressure, but the pulse rate declined an average of 42 per minute. During the inhalation of oxygen, the average oxygen capacity fell slightly, while all arterial oxygen contents, with one exception, rose. The femoral venous oxygen content fell in three instances and rose in all others. Only eight renal vein blood samples were obtained and of these the oxygen content rose in six and fell in two, the average being an increase. Portal venous oxygen contents rose in all experiments except one. The average oxygen content of blood from the right heart was increased. On the whole the increase in oxygen content of blood from various sites was not as great as in the experiments on hemorrhage. The order of increase in oxygen content of blood from the various regions was, from greatest to smallest, the portal vein, renal vein, femoral vein, femoral artery, and right heart. This order of increase is, as were the changes in hemorrhage, quite different from that order obtained as a result of the administration of oxygen in histamine shock. The average results of these experiments are to be seen in Table III.

DISCUSSION

As has been shown, the administration of high concentrations of oxygen to dogs in shock usually results in an increase in the average oxygen content of both arterial blood and venous blood returning from various regions. The magnitude of the effects of this on the mean peripheral oxygen tension may be estimated by a consideration of the oxygen dissociation curve for dog blood,[4] assuming, for the moment, constancy of hydrogen-ion concentration and that the mean venous oxygen tension is a function of the corresponding tissue tension. Under these conditions, in experiments in which shock was the consequence of hemorrhage, administration of oxygen resulted in an aver-

TABLE II

THE EFFECT OF THE ADMINISTRATION OF PURE OXYGEN ON SHOCK PRODUCED BY HISTAMINE
(AVERAGES OF THE RESULTS OBTAINED IN 7 EXPERIMENTS)

	B.P. IN MM. HG	PULSE RATE PER MIN.	RESPIRATIONS PER MIN.	HEMATOCRIT VOLUME %	O_2 CAPACITY VOLUME %	CO_2* AND O_2 CONTENT, VOLUMES PER CENT									
						FEMORAL ARTERY		FEMORAL VEIN		RENAL VEIN		PORTAL VEIN		RIGHT HEART	
						CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2
Controls	164/93	77	52	32.8											
115 min. after first histamine injection; total of 6 mg. administered subcutaneously	99/71	199	31	39.7	25.23	25.65	21.73	36.73	8.84	28.28	17.39	30.15	11.82	35.01	9.22
After 15 min. of inspiring pure O_2	106/80	178	34		24.85	30.57	22.58	39.62	10.84	31.38	18.59	37.40	12.72	38.56	10.39
Average change resulting from the inhalation of O_2	+7/+9	-21	+3		-0.38	+4.92	+0.85	+2.88	+2.00	+3.10	+1.20	+7.25	+0.90	+3.55	+1.17

*CO_2 content determinations were made in 3 experiments only.

TABLE III

THE EFFECT OF THE ADMINISTRATION OF PURE OXYGEN ON SHOCK PRODUCED BY TRAUMA
(AVERAGES OF THE RESULTS OBTAINED IN 11 EXPERIMENTS)

	B.P. IN MM. HG	PULSE RATE PER MIN.	RESPIRATIONS PER MIN.	HEMATOCRIT VOLUME %	O_2 CAPACITY VOLUME %	CO_2* AND O_2 CONTENT, VOLUMES PER CENT									
						FEMORAL ARTERY		FEMORAL VEIN		RENAL VEIN		PORTAL VEIN		RIGHT HEART	
						CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2	CO_2	O_2
Controls	176/100	72	66	34.3											
138 min. after trauma to the left posterior extremity	109/81	220	28	37.1	22.01	27.17	19.27	37.62	3.98	30.62	14.09	37.84	6.41	35.12	5.21
After 15 min. of inspiring pure O_2	108/79	178	33		21.75	32.52	20.23	38.98	5.07	35.26	15.31	39.21	8.22	42.20	5.92
Average change resulting from the inhalation of O_2	-1/-2	-42	+5		-0.26	+5.25	+0.96	+1.36	+1.09	+4.64	+1.22	+1.37	+1.81	+7.08	+0.71

*CO_2 determinations were made in 5 experiments only.

age estimated rise in oxygen tension of the femoral venous blood from 22 to 26 mm. Hg, an increase of 18 per cent. The estimated oxygen tension of renal and portal venous blood increased 20 and 17 per cent respectively. When histamine was employed to produce shock, the estimated oxygen tension of the femoral venous blood was increased 18 per cent; whereas, those of the renal and portal veins were increased 10 and 4 per cent respectively. Inhalation of oxygen in the experiments on traumatic shock resulted in an increase in the femoral venous oxygen tension of 13 per cent and an increase in the renal oxygen tension of 11 per cent. The oxygen tension in the portal vein was increased 19 per cent.

Although in making these calculations we have assumed constancy of blood hydrogen-ion concentration, actually this is not necessarily the case. In the first place gas analyses revealed that in most instances the CO_2 content of the blood rose during oxygen inhalation; and second, the fall in arterial pH accompanying this was directly measured with the glass electrode in several experiments, thus indicating clearly a considerable rise in alveolar CO_2 tension. Inasmuch as the absorbing power of the spirometer seemed adequate, it would appear that the respiratory resistance in our apparatus was responsible, although this is by no means certain. Similar evidences of progressive CO_2 excess were observed by Crafoord[5] during administration of oxygen under positive pressure to dogs in the course of thoracic operations carried out under intravenous anesthesia.

Moderate increases in CO_2 tension, such as those in our experiments, might be expected to increase still further the availability of oxygen to the tissues (i.e., increase the average tissue oxygen tension). This is a consequence of the Bohr effect, that is to say, the effect of increased CO_2 tension in increasing the percentage of oxyhemoglobin dissociated at a given oxygen tension.

The coefficient of oxygen utilization is the fraction of the total oxygen content of the blood which is given up to the tissues in the passage of blood through the capillaries. It is calculated by dividing the arteriovenous difference in volumes per cent by the arterial oxygen content in volumes per cent. Normally, it varies considerably for different tissues and for the same tissue in accordance with the degree of its activity and rate of blood flow. Best and Taylor[6] state: "Other things being equal, the slower the flow of blood through the capillaries the greater will be the quantity of oxygen given up to the tissues and the lower will be the oxygen content of the venous blood." Interpreted in terms of the coefficient of oxygen utilization, this means that, if the local tissue demand for oxygen remains the same, an increase in the coefficient represents a decrease in the rate of blood flow through the tissue and, conversely, a decrease in the coefficient represents an increase in the rate of flow. Referring to Table IV, it will

TABLE IV

THE AVERAGE CHANGE IN THE COEFFICIENT OF UTILIZATION OF OXYGEN RESULTING FROM THE INHALATION OF PURE OXYGEN*

	POSTERIOR EXTREMITY	KIDNEY	INTESTINES	BODY AS A WHOLE
Average change produced by inhalation of pure oxygen in shock produced by hemorrhage	-7%	-3%	-8%	-2%
Average change produced by the inhalation of pure oxygen in histamine shock	-8%	-3%	-3%	-5%
Average change produced by the inhalation of pure oxygen in traumatic shock	-5%	-3%	-9%	-3%

*The coefficient of oxygen utilization is calculated by dividing the arteriovenous difference by the corresponding arterial oxygen content. The latter is corrected for changes in oxygen capacity occurring during the experiment.

be seen that following the administration of pure oxygen there was an appreciable decrease in the average oxygen coefficient of utilization for all the regions studied. This decrease could be the result of either a decrease in the metabolism of the tissue or an increase in the rate of flow through the tissue. The former possibility appears unlikely and we are led to believe that there was an increase in the rate of blood flow through all of the areas studied.

This apparent increase of flow in the various parts should be manifested by a rise in cardiac output and, indeed, such was found to be the case in experiments in which this function was measured.* According to Best and Taylor,[6] an increased oxygen tension in the blood results in a slight diminution of the cardiac output; whereas, an increased carbon dioxide tension is usually accompanied by an increase in cardiac output. Sollman[7] states that capillaries are constricted by excessive oxygen tension and are dilated by excessive carbon dioxide tension. Inasmuch as both an increase in oxygen tension and an increase in carbon dioxide content of the blood occurred in most of our experiments, it is impossible to determine which factor was dominant; however, it was noted that there was usually a slight rise in the blood pressure and a decrease in the pulse. This, under ordinary circumstances, would mean an increase in cardiac efficiency and probably in output.

If one uses the average decrease in oxygen coefficient of utilization (Table IV) as a very rough measure of the quantitative change in rate of flow, one sees that there are variations between the average change in rate of flow from the same regions in the different types of shock. In the traumatic and hemorrhagic types of shock, the average decreases in oxygen utilization by the different regions bear a strikingly

*The determinations of cardiac output made prior to oxygen inhalation were performed with an air-filled spirometer.

similar relationship to each other; in shock produced by histamine this relationship does not hold. Thus one finds that the presumed increase in rate of flow is much less marked in the intestinal region in those experiments in which shock was produced by histamine.

The difference in the response to oxygen therapy of shock as produced by hemorrhage and by trauma and that produced by the injection of histamine further emphasizes the view that the alterations in the circulation are not identical in these types of peripheral circulatory failure.

SUMMARY

1. The effects of the administration of pure oxygen to dogs with mild peripheral circulatory failure produced by hemorrhage, trauma, and injection of histamine have been studied.

2. The inhalation of oxygen under these conditions results in a considerable increase in the amount of oxygen available to the tissues, as evidenced by a rise in arterial oxygen content and increases in venous oxygen content of blood from various parts. This availability may be further enhanced by concomitant increases in carbon dioxide tension.

3. The observations confirm the prevailing impression that inhalation of high concentrations of oxygen exert beneficial effects in the treatment of peripheral circulatory failure.

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A TECHNIQUE FOR TOTAL GASTRECTOMY

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THERE are many physicians and a few surgeons who believe that the operation of total gastrectomy is a very questionable procedure. This is based upon the following data: first, there is a very high immediate mortality directly attributable to the operation; second, practically all patients who survive the operative ordeal ultimately die from metastases arising from the gastric carcinoma; third, the dietetic restrictions which many such patients must observe following survival from the operation of total gastrectomy are such as to be incompatible with happiness and freedom from gastrointestinal discomfort.

All who have struggled in attempting to solve this problem must accept the first two objections as being valid. The third, however, is debatable. It is true that some patients who have survived a total gastrectomy are unable to carry out a dietetic regimen which results in complete freedom from gastrointestinal symptoms. On the other hand, we have had patients who, apart from eliminating a few specific articles of diet from their menu, had a return of appetite and achieved freedom from gastrointestinal distress for as long as two and one-half years.

The enthusiasm which the individual surgeon displays for this operative procedure will depend largely on his philosophy of life. If such philosophy demands that all efforts be used to prolong life, even though the effort be accompanied by grave immediate risk, and though the patient ultimately must die from carcinoma, providing he lives long enough, then such a surgeon must be an advocate of total gastrectomy. Our experience with total gastrectomy in nineteen cases represents efforts to restore continuity between the esophagus and the rest of the gastrointestinal tract by many combinations and permutations of anastomoses between stomach, duodenum, and jejunum. The mortality until recently has been due almost entirely to the technical difficulty of securing a satisfactory esophagojejunal anastomosis. In one case in which the patient survived an esophagoduodenal anastomosis, he was never able to achieve as great gastrointestinal comfort as we would wish.

The preoperative preparation of patients who are possible candidates for total gastrectomy must be adequate. This demands the restoration of the fluid and salt balance and the correction of the avitaminosis which is almost invariably present, due either to the patient's inability to take an adequate diet or to the fact that a diet deficient in vitamins has been prescribed. The hazards of an associated anemia can be controlled by means of blood transfusion.

Despite our belief that this operation is justifiable, the high primary operative mortality has made us pause, on many occasions, to question whether we were justified in asking patients to accept such an operative risk; yet, when it is realized that without excision of the carcinoma a distressing death awaits the patient, the attempt to relieve the symptoms becomes justifiable. The technique which is presented has been carried out in six cases, and in none of these has the primary cause of the still appalling primary mortality been due to the esophagojejunal anastomosis. One patient died of peritonitis, due to obstruction of the distal jejunum, the result of a jejunostomy which obstructed the jejunum. This obstruction resulted in a ballooning of the proximal jejunal limb to such a degree as to result in a leak at the esophagojejunal line of anastomosis. The second patient died from anuria following a transfusion. This unfortunate and still unexplained reaction occurred despite the most meticulous care in the laboratory in carrying out tests for determining compatibility of donor and recipient bloods. One patient died from coronary thrombosis when convalescent. One died from acute pancreatitis, the result of damage to the pancreas following a partial resection of this organ, which was involved in the neoplasm. One patient is still alive and well nineteen months after operation. A recent patient died forty-eight hours postoperatively, and this is the only case in which it was impossible to secure a post-mortem examination, and it is believed that this death was due to an overwhelming respiratory infection.

Of the other thirteen cases, there were four survivals. Three died of cardiovascular accidents, one of a cerebral embolus on the tenth postoperative day. This patient had a coincident removal of the spleen, and it would appear that the vascular accident was contributed to by the increase in platelets which followed the splenectomy. Since this experience we have avoided removal of the spleen wherever possible, despite the fact that the coincident removal of this organ greatly simplifies the technical procedure. If, because of accidental injury of the splenic blood supply, or because of the site of the growth splenectomy becomes necessary, the patient should be given heparin postoperatively in an effort to prevent a repetition of such an unfortunate vascular accident. One patient died of hemorrhage which came on suddenly forty hours postoperatively. Only one patient had a subphrenic infection, which occurred six weeks postoperatively, the result of a leak at the anastomosis. The other deaths were due to a leak at the esophagojejunal anastomosis.

This terrific mortality is not such as to make one proud of the results. It is presented to show the tenacity of purpose which is prompted by the firm belief that every effort should be made to extirpate a gastric carcinoma which, if left in situ, is inevitably fatal. This attitude

is further justified by the fact that in seven of these nineteen cases, or 36.8 per cent, there was no evidence of extension of the disease beyond the stomach and no metastatic disease in the adjacent lymph glands. The fact, then, that over one-third of the cases of gastric carcinoma are lethal solely because of the local extent of the disease, justifies the hope that a survival following a total gastrectomy may result in a prolongation of life, freedom from gastrointestinal distress, and a mental peace which will justify the high primary operative mortality. It is hoped that our future efforts as a result of the technical procedure to be presented may result in a lower mortality. This hope is justified by our experience with the last six cases, in which in only one instance was the anastomosis a factor in the ultimate mortality, and this only indirectly, because of a technical error in the performance of a jejunostomy.

Fig. 1.—The stomach has been divided from the duodenum. The illustration shows the method of increasing the infradiaphragmatic length of the esophagus by freeing it from the margins of the diaphragm by inserting the finger along the esophagus into the mediastinum. The esophagus at a point eighteen inches from the duodenojejunal juncture is fastened to the diaphragm behind the entrance of the esophagus by means of interrupted sutures.

DETAILS OF THE OPERATIVE PROCEDURE

The abdomen is opened by displacing the upper right rectus laterally by a right paramedian incision. A survey of the intraperitoneal lesions must be carried out before any further direct attack on the gastric neoplasm is made. Particularly one must be certain that no metastases are present in the pouch of Douglas in the female, or in the rectal shelf in the male; that the liver is free from metastases; that the carcinoma has not invaded surrounding structures; that the glandular involvement is not so extensive as to be incapable of removal. If the disease is limited to the stomach and adjacent lymph glands, and the involvement of other structures does not preclude its excision, then adequate exposure must be provided. Transverse divi-

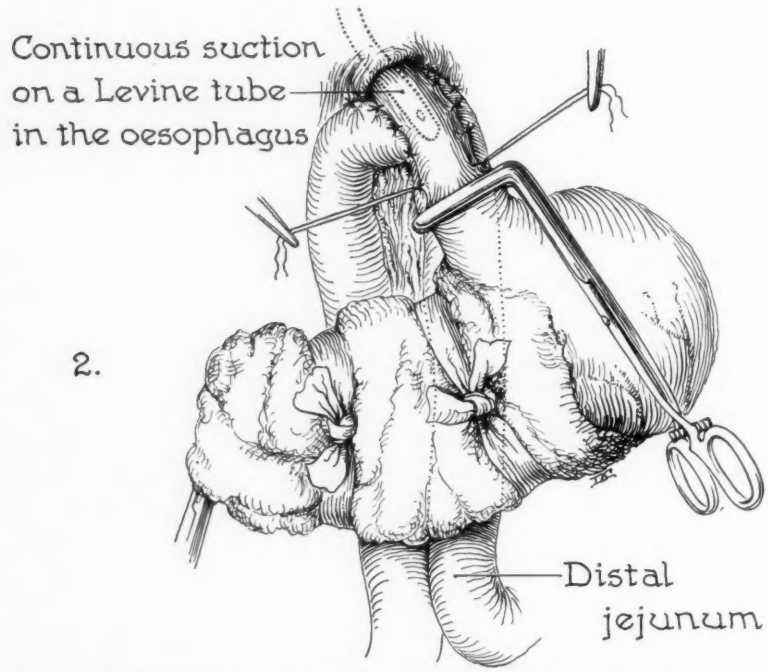
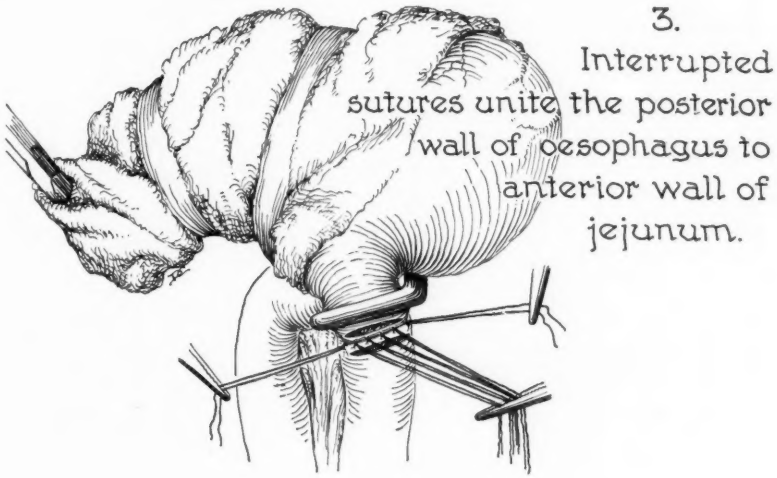


Fig. 2.—The infradiaphragmatic portion of the esophagus is placed on the anterior surface of the distal limb of the jejunum and fastened there by means of interrupted silk sutures. The Levine tube in the esophagus by means of attachment to suction apparatus keeps the esophagus free from accumulated secretions.

sion of the left abdominal wall midway between the ensiform and the umbilicus is a great asset. The maneuver of mobilizing the left lobe of the liver as popularized by Turner adequately exposes the entrance of the esophagus to the peritoneal cavity. The great omentum is removed in its entirety and the greater and lesser curvatures of the stomach mobilized and the duodenum divided just distal to the pylorus. The technique of this mobilization and closure of the duodenal stump has been previously presented.[1] When the stomach has been freed from the duodenal end, it is wrapped in gauze which is tied with heavy

tape. By downward traction, using the stomach as a handle, the finger is inserted between the esophagus and the opening of the diaphragm. This will isolate both vagi, the division of which will permit the mobilization of the esophagus to a surprising degree. Further separation of the periesophageal structures by blunt gauze dissection will often make it possible to draw down the esophagus a distance of two inches below the opening in the diaphragm. When this has been accomplished, the suggestion of Allen[2] of suturing the jejunum to the undersurface of the diaphragm by means of interrupted sutures is carried out (Fig. 1). A point in the jejunum approximately eighteen inches from the duodenojejunal junction is selected and the jejunum is brought up in front of the transverse colon to be fixed to the diaphragm. The procedure advocated by Allen adequately fixes the



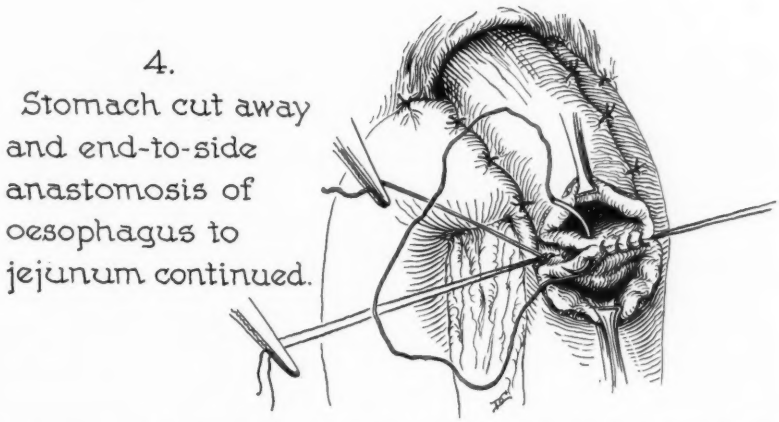
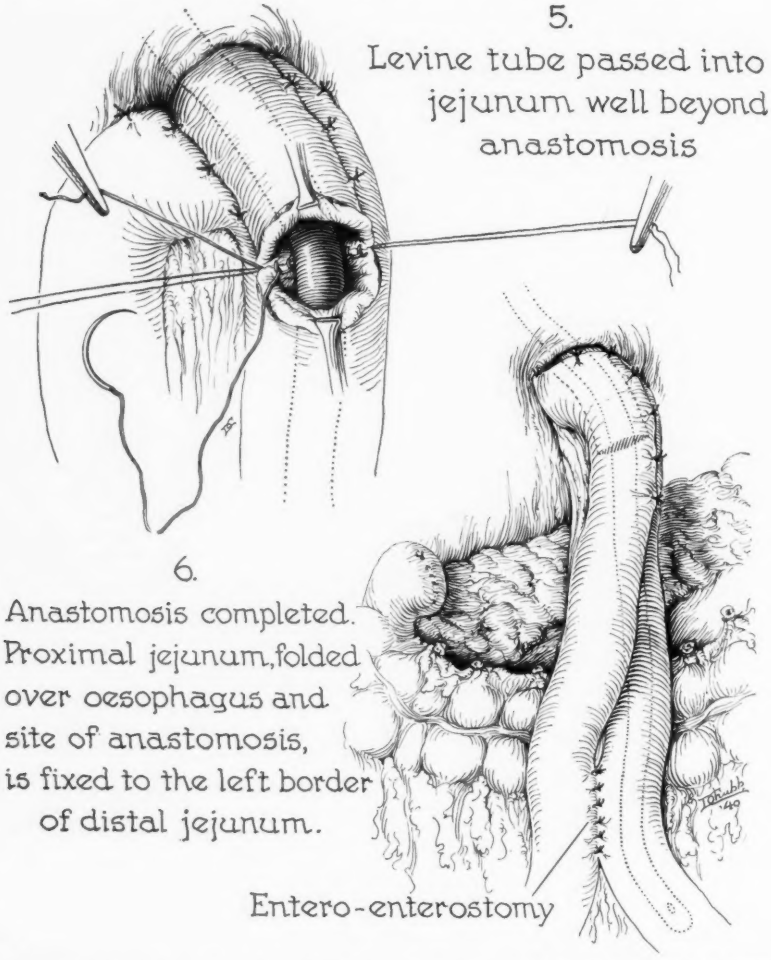


Fig. 3.—If the infradiaphragmatic portion of the esophagus is unduly short, it is advantageous to leave the stomach attached to the esophagus while interrupted sutures unite the posterior wall of the esophagus to the anterior wall of the distal limb of the jejunum. The two lateral sutures are held in hemostats and act as stay sutures while the esophagojejunal anastomosis is completed.

Fig. 4.—Here the stomach is cut away and the mucous membranes of the stomach and jejunum are being united.

jejunum and prevents the weight of jejunal contents from being a factor in creating tension on the new esophagojejunal anastomosis. When the jejunum is firmly anchored to the diaphragm, the infradiaphragmatic portion of the esophagus is then fixed by means of interrupted sutures to the anterior surface of the distal limb of the jejunum. Usually three or four such sutures on either side are sufficient to achieve this, the most distal suture on either side being held in hemostats to act as guy sutures (Fig. 2). The esophagus then may be divided, great care being taken to keep up continuous suction by a Levine tube which had


5.
Levine tube passed into jejunum well beyond anastomosis
6.
Anastomosis completed. Proximal jejunum, folded over oesophagus and site of anastomosis, is fixed to the left border of distal jejunum.
Entero-enterostomy

Figs. 5 and 6.—When the posterior layer of mucous membrane sutures is completed, the Levine tube is passed down further into the distal jejunum well past the esophagojejunal anastomosis and the anterior layers of the anastomosis are completed. The proximal jejunum is then folded over the front of the esophagus and the esophagojejunal anastomosis and united to the lateral margin of the distal limb of the jejunum. By this maneuver the esophagus and the esophagojejunal anastomosis are completely encircled by the jejunal loops. This contact of peritoneum to peritoneum ensures healing to a greater degree than the contact of the bare esophagus to the jejunum. This maneuver completely obstructs the proximal jejunal loop and makes an enteroanastomosis necessary. During this anastomosis the Levine tube is passed further down into the distal jejunum to make possible direct jejunal feeding early in the patient's convalescence.

been passed into the stomach before the operation, and which is now withdrawn to a point in the esophagus just proximal to the line of division. If it has been possible to bring down only a short infradiaphragmatic portion of the esophagus, it may be advantageous to retain the stomach as a means of downward traction while interrupted sutures unite the posterior wall of the esophagus to the anterior wall of the jejunum (Fig. 3). The esophagus then must be divided and the jejunum is opened. The Levine tube is then passed down into the

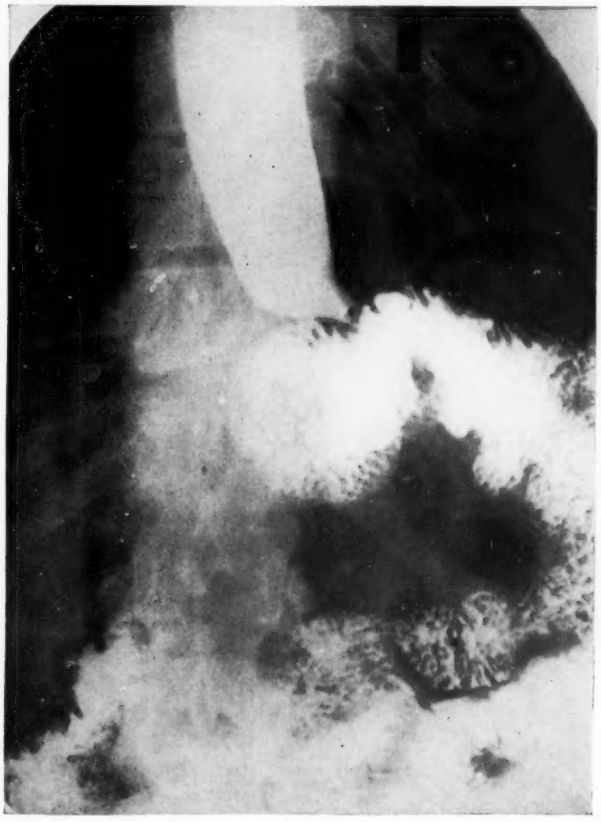


Fig. 7.—Case of Mrs. C. B. (No. A51111), total gastrectomy, July, 1938. X-ray study, Aug. 15, 1938, showed evidence of efficient anastomosis. Alive and well, February, 1940.

distal jejunum after the posterior layer of the anastomotic suture has been completed (Fig. 4). The anterior layers of the anastomosis are completed in the usual manner, making a very satisfactory end-to-side stoma between the lower cut end of the esophagus and the anterior wall of the distal limb of the jejunum. When the anastomosis is completed, the proximal jejunal loop is then rolled laterally across the esophagus and sutured to the left lateral margin of the distal limb of the jejunum. This completely surrounds the infradiaphragmatic portion of the esophagus with the jejunal loops, and very firmly covers and supports the end-to-side jejunoesophageal anastomosis, as indi-

cated in Fig. 5. This maneuver completely obstructs the proximal jejunal loop, and therefore an enteroenterostomy must be carried out between the proximal and distal jejunal loops. During the performance of this anastomosis, the Levine tube is passed on into the distal limb of the jejunum past the enteroenterostomy (Fig. 6). The abdominal wall then may be closed in layers without drainage. A stitch placed in the patient's cheek is tied around the indwelling Levine tube, in order that the patient's immediate postoperative restlessness will not result in removal of this tube. While the interrupted sutures indicated in the text and in the diagrams may be accomplished by means of catgut sutures, I prefer to use silk. The minimal trauma and tissue reaction about silk commends it to a very great degree in this operation.

Immediately following operation, the fluid balance is maintained by means of the intravenous administration of 5 per cent glucose in saline solution and 5 per cent glucose in distilled water, 1,500 c.c. of each in twenty-four hours. Five hundred cubic centimeters of blood are given during the operative procedure. No food or fluid is given by mouth, but the patient is allowed to take ice chips. The oral cavity is sprayed with liquid paraffin, which adds greatly to the patient's comfort by avoiding a dry mouth, and it also allays the irritation from the indwelling Levine tube. In addition it is a real factor in the prevention of postoperative parotitis. At the end of twenty-four hours 10 per cent glucose in saline solution can be introduced into the jejunum through the Levine tube by the drip method at the rate of 125 c.c. an hour. At the end of forty-eight hours, the type of feeding and management as advocated in the tube treatment of gastric ulcers is applicable here.[1] The x-ray appearance of the anastomosis is shown in Fig. 7. This patient was operated upon July, 1937, and to date is well and free from recurrence and suffering no gastrointestinal distress.

CONCLUSIONS

1. Over one-third of the patients submitted to total gastrectomy had no histologic evidence of metastasis in the regional lymph glands or in other intraperitoneal structures.

2. Such an incidence of local disease justifies the operation of total gastrectomy, despite the high primary postoperative mortality.

3. The survival from this procedure is compatible with happiness, negligible dietetic restrictions, and freedom from gastrointestinal distress.

4. The technique of esophagojejunal anastomosis here presented offers a method which, it is hoped, will decrease the immediate postoperative mortality.

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THE SURGICAL TREATMENT OF PRIMARY DUODENAL DIVERTICULA

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THE history of the surgery of primary duodenal diverticula is a relatively recent one. It dates back for only twenty-five years when Forsell and Key[17] performed the first deliberate attack on a primary duodenal diverticulum. Diverticula secondary to duodenal ulcer had been recognized and treated for a longer period. Here, however, the operation was directed against the ulcer, and the associated diverticulum was a mere incident.

Although primary duodenal diverticula are relatively common, indications for surgery upon them have not been of great frequency. In the University of Rochester Hospitals primary diverticula of the duodenum have been recognized in at least thirty-three individuals but operation has been performed in only two instances.

CASE REPORTS

CASE 1.—I. B. (No. 161042), a 57-year-old woman, was admitted to the Strong Memorial Hospital on Jan. 12, 1940. For the past eight or nine years she has had frequent attacks of dull aching in the right upper quadrant. The pain radiated to the right posterior chest wall and right shoulder. During the last two months the attacks had increased in frequency, severity, and duration. The distress was almost constant although mild. The only other symptom noted was frequent gaseous eructation. In her past history the patient had an appendectomy and bilateral salpingo-oophorectomy twenty-nine years ago. There were attacks of renal colic and pyuria ten years ago.

Examination was negative with the exception of an area of tenderness on deep pressure in the right epigastrium just above and slightly lateral to the umbilicus.

Laboratory examinations showed a rather large gall bladder with poor emptying after a fatty meal. There were no stones visualized. The gastrointestinal series revealed a diverticulum of the descending duodenum (4.5 by 5 cm.) with no retention of barium. On fluoroscopic examination the tenderness previously noted was found to be directly over this diverticulum. The diverticulum seemed to be close to the region of the common duct entrance. There were also several olive-sized diverticula of the first jejunal loop made out.

At operation, the gall bladder appeared to be normal. At least six diverticula were demonstrated in the jejunum. These had no evidences of inflammation or obstruction. The duodenum was mobilized by dividing the peritoneum along its lateral edge and rotating the viscus toward the midline. The diverticulum was demonstrated. It was freed from its position between the common duct and head of the pancreas until it could be brought into the peritoneal cavity at the right side of the descending duodenal loop. The mouth admitted the index finger readily. The superior pancreaticoduodenal artery ran over the neck of the sac. The opening was intimately associated with the papilla of Vater. It was con-

sidered better surgery to treat this diverticulum conservatively. Accordingly it was left in situ in the belief that it would not trap duodenal contents and would no longer exert pressure on the common duct junction.

Postoperatively the patient made a good recovery. She has been free from symptoms for two months. Time will tell whether the surgeon's judgment was good.

CASE 2.—R. D. (No. 104466), a 60-year-old woman, was admitted to the Strong Memorial Hospital on Dec. 10, 1939. Two days previously she had a sudden onset of severe epigastric pain, starting shortly after breakfast. It was crampy in nature and centered more in the right upper quadrant. It was accompanied by chills, fever, and vomiting. There was radiation of pain to the back but not to the right shoulder. The pain subsided in five hours, but anorexia, malaise, fatigue, and nausea persisted. The skin was noted to become yellowish. The urine was dark; the stools were not observed. There was no previous history of similar nature. The rest of the history had no bearing on this illness.

Examination showed an acutely ill, irritable, drowsy person with moderate icterus. There was tenderness in the right upper quadrant but no spasm. The examination was negative in other respects. The temperature was normal, the pulse was 80. Positive laboratory findings were bile and acetone in the urine. The icteric index was 13. Cholecystogram showed poor concentration of the dye but nothing that could be interpreted as gallstones. Gastrointestinal series demonstrated a small diverticulum (4 by 4.5 cm.) of the descending loop of the duodenum. There was also a large diverticulum (4.5 by 6 cm.) coming off the ascending portion near the ligament of Treitz. There was tenderness over this latter diverticulum, and retention of barium at the four-hour examination. Diagnosis: Cholecystitis probable; diverticula of the second and third portions of the duodenum. The patient's acute symptoms quickly subsided on a smooth low fat diet and atropine. She was discharged ten days after admission. She was readmitted on Feb. 27, 1940. In the interval she had remained weak and was slow in regaining her strength. She began to feel better about one week before this second admission. Four days before, she had another attack of severe epigastric pain, lasting five hours. It required morphine for relief. There was no vomiting but persistent nausea. No icterus was noted. She has had headaches and soreness between the shoulder blades. Upon examination there was tenderness in the right upper quadrant, but nothing else of significance.

At operation, a thickened gall bladder was removed. It contained stones. The diverticulum of the third portion of the duodenum was exposed by dividing the gastrocolic omentum and entering the lesser peritoneal sac. The fourth portion of the duodenum was isolated. The pancreas was lifted up from it and the duodenum traced to its third portion. At this place the neck of the diverticulum was isolated. The pouch was freed, the neck of the sac divided. The defect was closed first with a Parker-Kerr stitch and then with a purse-string suture inverting the mucosa. A third layer of interrupted silk sutures in the serosa was used. Operation was done by Herman Pearse.

Recovery was uneventful. Patient is well to date.

It is apparent from a close study of these two records that perhaps in these cases operation was necessary because of other pathologic states. In Case 1 there was a mechanical factor of back pressure on the common duct. The patient had been told elsewhere that she had a diseased gall bladder. This, coupled with her fear that it was malignant, made an exploration almost obligatory. In Case 2 the presence of a pathologic

gall bladder probably accounted for the symptoms. The diverticulum was removed in order to eradicate a potential source of danger.

A review of the literature on this subject leaves an impression that primary diverticula of the duodenum in most cases do not cause symptoms. The majority of the diverticula arise in the region of the ampulla of Vater. The outpouching occurs through a potentially weak area in people beyond 25 years of age, most frequently in the late 40's or 50's. The opening is usually large; the sac empties easily because it has dependent drainage. The position of the sac is nearly always retroperitoneal and on the concave side of the duodenal loop. There is thus a support from the peritoneum, the pancreas, and the duodenal wall itself so that these herniations cannot easily sag or kink at the neck of the sac until they have attained a large size. Some of them are completely surrounded by pancreatic tissue. They may contain accessory pancreatic tissue in their walls.

There is evidence, however, that in some instances symptoms have been due to the diverticulum. There are enough well-documented cases to indicate that removal of the diverticulum has been followed by a complete absence of the distress which prompted operation. In such cases symptoms may have followed a gastric, duodenal, biliary, pancreatic or intestinal stasis pattern. Typical examples can be quoted in support of each of these. There is thus no definite clean-cut picture by which a clinical diagnosis can be established. But, if such a patient with symptoms referable to the upper abdomen can be shown to have negative examinations for the stomach, duodenum, biliary tree, pancreas, and upper intestine, the diverticulum may then be presumed to be at fault. If also it can be shown to have tenderness over it on fluoroscopic examination and stasis of the barium in its sac, the evidence becomes stronger. In some cases the duodenum above the diverticulum may show evidence of partial obstruction. This is manifested by dilatation of the loops, an upset in the peristaltic regularity, and perhaps pylorospasm.

The presence of inflammation can manifest itself as a localized diverticulitis; or as an extension into the biliary tract, pancreas, or adjacent structures. This may give rise to secondary cholangitis or cholecystitis, pancreatitis, etc.[2, 6, 19] The presence of jaundice has been noted frequently in these cases. Diverticulitis may be catarrhal, suppurative, gangrenous. There have been perforations with local abscess or peritonitis (Table V).

Finally, there is a remote chance of neoplastic change in a duodenal diverticulum. Morrison and Feldman[42] described a carcinoma in such a case; and Mendillo and Koufman,[38] a leiomyosarcoma in another.

There is a justification for surgery of duodenal diverticula upon the following grounds: (A) mechanical: (1) giving rise to symptoms from

local stasis in the diverticulum, (2) giving rise to symptoms from partial obstruction to the biliary tract, pancreatic ducts, or duodenum; (B) inflammatory: (1) local diverticulitis, perforation, abscess, peritonitis, (2) secondary inflammation of the biliary tract (jaundice), pancreas, duodenum, retroperitoneal tissues; (C) neoplastic change.

It is possible also that the presence of diverticula may upset the smooth running of the gastrointestinal tract by disturbances in the nervous control.

Operations upon duodenal diverticula have been of several different types. First of all, in very difficult cases a direct attack may be avoided by resorting to a side-tracking operation. This has been the solution used by many well-known surgeons, no attempt being made to expose the diverticulum. Such operations as pyloric division with a Polya type of anastomosis have been done. In the absence of a pathologic lesion in the antrum or in the first part of the duodenum such an operation is not to be recommended.

Direct approach to the diverticulum varies with its situation. When the diverticulum is in the descending loop (second portion of the duodenum), its position is nearly always retroperitoneal. It frequently is peri-Vaterian and in close relationship to the openings of the common duct and the pancreatic ducts. At times it is embedded in the pancreas. It is on the concave side of the loop and posterior. Many times the main pancreaticoduodenal vessels run directly across the neck of the sac. In a number of instances surgeons have failed to find such a diverticulum at operation. This was more frequent when these cases were first being explored.

The approach from the medial side of the duodenal loop is difficult and annoying. There are many small vessels entering the tissues about the head of the pancreas. Nevertheless some surgeons have made this approach successfully, even dividing the pancreas over the sac in order to identify it.

The approach from the lateral border of the duodenum is better. The peritoneum is divided along the lateral border of the duodenum. This is a relatively bloodless area. The surgeon then mobilizes the duodenum towards the midline. He can turn it over, exposing the posterior wall. The duodenum can be exposed posteriorly all the way to Treitz's ligament in this manner. It is the type of approach recommended by Ladd[31] and by Morton and Jones[43] for congenital duodenal obstructions. If very small the diverticulum can be inverted without excision.[22] If larger, the diverticulum is freed from the surrounding tissues by careful dissection. The neck is ligated, the sac excised, and the stump inverted into the duodenum. Reinforcing sutures may be used. When the neck is wide the defect may be closed in a transverse direction. The pancreaticoduodenal vessels may be pushed aside and

preserved. If the opening of the sac encroaches upon the ampulla, it may be dangerous to excise it.

Maclean[36] described a method which possesses merit. The duodenum is opened directly on its anterior surface in the descending portion. The neck of the sac is found and its relations to the ampulla visualized. The surgeon inserts his finger into the sac through its neck. It is then

TABLE I

DIVERTICULA DUODENUM, DESCENDING LOOP, SECOND PORTION, NO INFLAMMATION

YEAR	AUTHOR	SEX	AGE	OPERATION	RESULT
1915	Forsell and Key	Female	41	Resection, suture	Well
1919	Siegrist	Male	48	Resection, suture; adherent to pancreas	Well
1925	Lecene	Female	52	Resection, suture	Well
1926	Stiles*			Resection, suture	Well
1926	Kinard and Vandel	Male	68	Appendectomy; resection, suture	Well
1926	Grégoire	Female	60	Resection, suture	Well
1929	McQuay				
	Case 3	Female	34	Resection, suture	No change
	Case 6	Female	40	Resection from pancreas; suture; degastroenterostomy	Well
1931	v. Friedrich	Male	57	Resection, suture	Not stated
1932	Hanke				
	Case 2	Female	48	Resection, suture	Symptoms recurred
	Case 3	Female	43	Posterior gastroenterostomy; diverticulum not disturbed	Well
1932	Harris	Female	49	Resection, suture; stone in diverticulum	Well
1933	Sullivan†				
	Case 1	Female	56	Resection from pancreas, suture	Local pancreatic abscess draining
	Case 2	Male	63	Diverticulum inverted; pylorectomy posterior gastroenterostomy	Well
1934	Edwards	Female	54	Resection, suture	Well
1936	Tanner	Female	65	Resection from pancreas, suture	Well
1936	Fletcher and Castleden				
	Case 1	Female	64	Resection, suture	Well
	Case 2	Female	52	Resection, suture	Well
	Case 3	Female	42	Resection, suture; adherent to pancreas	Well
1936	Albers	Female	40	Resection, suture; cholecystectomy for gallstones	Well
1938	Mendillo and Koufman	Male	49	Resection, suture; leiomyosarcoma in sac	Well
1939	Hellner	Female	28	Resection, suture	Well

*See Spriggs and Marxer.
†See Barnes.

TABLE II

DIVERTICULA DUODENUM, THIRD PORTION, NO INFLAMMATION

YEAR	AUTHOR	SEX	AGE	OPERATION	RESULT
1917	Basch	Female	36	Through mesocolon; resection, suture, posterior gastroenterostomy	Well
1922	Downes Case 2	Female	53	Through mesocolon; resection, suture	Well
1927	Maclean Case 4	Female	?	Resection, suture	Well
1927	Jacquelin and Quénu	Male	57	Through mesocolon; resection, suture	Well
1938	Guthrie and Brown	Female	50	Resection, suture; degastroenterostomy	Well

easy to dissect it from the surrounding tissues. The diverticulum is inverted into the duodenum. Its neck is ligated and it is removed. The opening in the anterior duodenal wall is repaired by suturing it in a transverse direction. This method is especially useful when the diverticulum is embedded in the pancreas.

When the diverticulum is in the third or fourth portion of the duodenum, it is still relatively inaccessible. It can be demonstrated by approaching this part of the duodenum through the transverse

TABLE III

DIVERTICULA DUODENUM, FOURTH PORTION, NO INFLAMMATION

YEAR	AUTHOR	SEX	AGE	OPERATION	RESULT
1922	Robineau and Gally	Female	39	Through mesocolon; resection, suture; attached to pancreas	Well
1927	Larimore and Graham	Female	63	Through mesocolon; had to cut Treitz ligament; resection, suture	Died, streptococcic peritonitis; no leak
1927	Maclean Case 3	Male	37	Through mesocolon behind pancreas; resection, suture	No follow-up
1927	Krogius	Female	64	Through mesocolon; adhesions to jejunum; resection, suture	Well
1928	Lund	Female	63	Through mesocolon; resection, suture; accessory pancreas present	Well
1933	Denis	Female	60	Through mesocolon; resection, suture	No follow-up
1933	Cromie	Female	38	Through mesocolon; resection, suture	Well
1933	Barnes	Female	58	Through mesocolon; resection, suture	Well
1936	Christidi	Male	32	Through mesocolon; resection, suture	Well

mesocolon. The retroperitoneal tissues are then divided. The duodenum is exposed from its under surface. The diverticulum is usually behind it and between the duodenum and the pancreas. Or it may be in the pancreas itself or behind this organ. It may be necessary to divide Treitz's ligament in order to get complete exposure.

In every case of diverticulum of the duodenum at operation a thorough investigation of the abdominal organs should be carried out. There is always a possibility that the symptoms are due to some associated pathologic lesion, the diverticulum being an incidental discovery.

Results from surgery of the duodenal diverticula are good as reported in the literature. Relief had been obtained in 80 per cent of the cases reviewed. In 8 per cent no follow-up was given; in 6 per cent the symptoms were not relieved. In one patient following operative removal a localized pancreatic abscess formed and was still draining at the time of the report. Drainage was used in 12 per cent, but these include the acute diverticulitis cases where it was indicated. In the uncomplicated resection there is no need for drainage unless the tissues have been severely damaged in the operation. Death occurred in 6 per cent. In two of these there were acute perforations; in the third, a streptococcus peritonitis.

Tables I-V were made up from articles consulted in the preparation of this report. There may be other contributions which have been overlooked, as not every reference could be followed up. Many diverticula associated with duodenal ulcer were eliminated as these represent secondary diverticula of the traction type. There were also

TABLE IV

DIVERTICULA DUODENUM, MULTIPLE, NO INFLAMMATION

YEAR	AUTHOR	SEX	AGE	OPERATION	RESULT	SITE
1920	Clairmont and Schinz Case 2	Male	36	Excision with wall; transverse suture	Well	2 diverticula in third portion
1922	Downes Case 3	Female	39	Through mesocolon; could not find; then mobilized descending duodenum; resection, suture	Well	2 diverticula in third portion
1928	Heidecker	Male	54	Inverted	Well	Multiple in duodenum and jejunum
1929	McQuay Case 10	Female	78	Duodenotomy; resection, suture; retraction of mesocolon; resection, suture	Well	1 diverticulum in second portion, head pancreas 1 diverticulum in third portion
1932	Hanke Case 1	Female	43	Resection, suture	Well	3 diverticula in second portion

TABLE V

DIVERTICULA DUODENUM, INFECTION, ACUTE AND CHRONIC

YEAR	AUTHOR	SEX	AGE	SITE	OPERATION	PATHOLOGY	RESULT
1920	Moore	Male	58	Descending loop (II)	Resection, posterior gastro-enterostomy	True diverticulum; moderate chronic inflammation	Well
1923	Maclean	Female	58	Desc. loop (II)	Duodenotomy, resection; diverticulum, drainage	Chronic pancreatitis	Well
1923	Huddy	Female	27	Desc. loop (II)	Resection, drainage	Gangrenous pouch; edema, retroperitoneal tissues	Well
1925	Butler and Ritvo Case 1	Male	40	Junction (I and II)	Inverted; reinforced	Markedly inflamed diverticulum	Well
1926-7	Monsarrat	Female	58	Desc. loop (II)	Resection, drainage	Perforated diverticula, *B. coli* abscess	Well
1930	Lucinian	Female	36	Desc. loop (II)	Resection	Perforation into head pancreas walled off inflamed reaction	Well
1933	Costello Case 1	Male	37	Jct. (II and III)	Inverted	Marked peridiverticulitis	Well
1938	Beaver	Male	54	Desc. loop (II)	Abdomen drained; diverticulum not found at operation	Acutely inflamed diverticulum; ruptured apex into head pancreas	Died
1939	Boland	Male	59	Desc. loop (II)	Appendectomy; cholecystectomy	Perforated diverticulum; abscess head pancreas	Died

a large number of excellent reviews on the diagnosis, pathology, and x-ray appearances of these diverticula. These have not been included in the bibliography as they made no contribution to the surgical treatment.

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THE PROBLEM OF SURGICAL ARREST OF MASSIVE HEMORRHAGE IN DUODENAL ULCER*

The Technique of Closing the Duodenum

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SURGEONS and internists alike, interested in and concerned with the vagaries of ulcer, have related that they have not had occasion to resort to direct surgical means for the arrest of massive hemorrhage in bleeding ulcer (Bier,[7] Hurst and Ryle,[17] Krönlein[18]). Up until quite recently this seemed to be almost universal experience; namely, that bleeding from an ulcer could be controlled by conservative means in almost all cases. For many years, however, Finsterer,[8, 9] of Vienna, has been insisting that, if bleeding continued beyond forty-eight hours, recourse should be had to surgery. In this country, Allen, of Boston, was the first to insist on a program of direct operative attack for threatening bleeding. Since these expressions have appeared, many clinics have taken occasion to study their own experience with reference to massive bleeding (Hinton,[15, 16] Pfeiffer,[23, 24] Snell[26]). Whereas previously it was believed on every hand and stated frequently that death from hemorrhage was a rare occurrence in ulcer, it is becoming more and more apparent that the lives of a fairly large number of patients with ulcer are lost through the agency of hemorrhage.

At the Municipal Hospital in San Francisco, Goldman[11, 12] found that of 349 patients admitted because of gross hemorrhage 31 (11.1 per cent) died of exsanguination, while an additional 17 (4.9 per cent) died of complications initiated by bleeding. La Due[19] reported the experience of the Minneapolis General Hospital, noting that 8 of 82 patients with bleeding ulcer died, a mortality of 9.8 per cent. Bergh, Hay and Trach[6] have summarized the experience of the Minnesota University Hospital, observing that 10 per cent of 70 patients treated conservatively for massive hemorrhage from ulcer died. In 2,565 collected cases of massive hemorrhage from ulcer treated conservatively, they found the mortality to be 10.2 per cent.

INDICATIONS FOR OPERATION

It is to be remembered that it was a long time after McBurney[20] first emphasized the necessity for early operation in acute appendicitis that surgeons began to have the opportunity of removing the

*The researches presented here were supported by grants of the Graduate School of the University of Minnesota and the Committee on Scientific Research of the American Medical Association, and by a grant for technical assistance by the Works Projects Administration, Official Project No. 665-71-3-69, Sub-project No. 58.

appendix before it was ruptured. The fallacy of the widely-held belief that patients with ulcer die rarely of hemorrhage has just been exposed. Finsterer's dictum of operation if bleeding continues after forty-eight hours of conservative treatment is not likely to be put into immediate effect in a large number of medical and surgical clinics in this country. Both internists and surgeons are aware of the magnitude of the operative procedure necessary to arrest bleeding. At the same time, they know that in a certain number of instances bleeding will cease spontaneously. Further, both internists and surgeons wish objective proof that those who attempt the surgical arrest of hemorrhage from bleeding ulcer are able to carry such procedures through with a reasonable mortality.

A clearer definition of the indications for operative intervention is urgently needed. Meulengracht,[21] who puts much emphasis on the value of frequent feedings to diminish the hazards of bleeding, admits having allowed nine patients to die of hemorrhage without submitting any to the surgeon. Following the example of Andresen[4] (1927) a number of American internists have fed ulcer patients with bleeding ulcer frequently (La Due[19]), but without the same degree of success reported by Meulengracht. Patients suffering from massive hemorrhage are often too ill to eat and attempts at feeding with a duodenal tube succeed frequently in ascertaining that gastric stasis is present. In such instances, during the trial period, when it is being determined whether operation should be done, it is the custom in this clinic to apply suction to an indwelling tube. By this means, hydrochloric acid, the agent which activates the bleeding, may be removed about as effectually as it is neutralized by the ingestion of food, with the additional advantage that the nausea of gastric stasis is obviated. Gordon-Taylor,[13, 14] who has had a large experience with the operative management of massive hemorrhage from ulcer, states that bleeding continuing after seventy-two hours of conservative treatment carries a risk of 78 per cent.

SIGNIFICANCE OF SHOCK

When an ulcer bleeds, blood may be lost slowly and gradually or quickly, depending on the size of the vessel that is eroded. In the instances of bleeding duodenal ulcer reported herewith that were subjected to operative intervention, an opening in the gastroduodenal artery was the uniform finding in those instances in which repeated bleeding to shock levels occurred. In other words, the craterous ulcer on the posterior duodenal wall had eroded through the duodenal wall completely. Perforation onto the gastroduodenal artery, which overlays the pancreas at this position, was the usual finding at operation. The artery, in turn, was eroded by the hydrochloric acid of the gastric juice with ensuant hemorrhage.

The significance of the occurrence of shock in bleeding ulcer cannot be emphasized too strongly. In all patients in whom it is difficult to sustain a satisfactory blood pressure, despite transfusion, it is apparent that blood is being constantly lost through a fairly large opening. Such patients in my opinion should be subjected early to operation. By choice, I would transfuse such patients and prepare for immediate operation. It is only fair to say, however, that, whereas such is my thought upon the matter, as a matter of fact, the patient reported here who was submitted earliest to operation after the onset of hemorrhage had bled for ninety-six hours (Case 1). In the other six patients of the series the time interval between onset of bleeding and operative intervention was twenty-four, twenty-three, eleven, twenty, eight, and seventeen days, respectively.

It is obvious that in all clinics where such operations are undertaken, internist and surgeon together must go through a proving period, during which time both become better acquainted with the limitations and advantages of conservative and operative management.

It must not be forgotten in patients transfused repeatedly for bleeding and in whom a second, third, or fourth episode of bleeding occurs that mere replacement of blood loss fails to afford the surgeon a patient well fortified to withstand the exigencies of a formidable operative procedure. Hemorrhage and depression of arterial pressure initiate a set of physiologic upsets that the administration of fluid and blood does not repair at once. This lag, exhibited by therapeutic procedures in catching up with the disturbed mechanisms which they are intended to relieve, must be appreciated more fully both by internist and surgeon. A patient who has bled to a critical level of blood pressure but once, granted immediate and full restoration of blood loss, is undoubtedly in a better position to withstand operation than the patient who has bled to shock levels repeatedly.

In the patient whose ulcer bleeds slowly but without the blood pressure falling to shock levels, the necessity for operation is not so urgent. Yet, the importance of not delaying too long is to be heeded here, too. It is significant that Finsterer[9] is able to report a mortality of 5 per cent in those patients submitted to operation within forty-eight hours of the onset of hemorrhage. In the group operated upon after the elapse of longer intervals the mortality was 30 per cent.

AGE

In the literature one gathers the impression that it is only the patient over 50 years of age who is likely to bleed. In the group of patients with massive hemorrhage reported here, there was one 24 years of age (Table I, Case 2) and one 36 years of age (Case 4). The oldest patient in the group was 80 years old. Fatal bleeding from a duodenal ulcer in the newborn has been reported. It is obvious, there-

fore, that young patients with flexible arteries may bleed briskly or die of hemorrhage and that youth alone does not constitute assurance that bleeding will stop without operation. In other conditions in which openings in arteries exist, one does not hear that only the patient with an arteriosclerotic vessel runs a big risk of dying of exsanguination.

OPERATION

Two of the patients in the present group were subjected to preliminary gastroenterostomy because of pyloric obstruction associated with the bleeding. In one instance (Case 1) a direct attack upon the bleeding point became necessary five weeks later; in the other case (Case 2) division of the duodenum and gastric resection was undertaken seven days later because of recurrence of bleeding which threatened life. The futility of gastroenterostomy to relieve massive bleeding from ulcer should be regarded as established.

In the patients reported here, a direct attack has been made on the bleeding point. Steep Trendelenburg position with transfusions of large quantities of blood prior to and during operative procedure have been employed regularly. Cyclopropane has been the anesthetic agent, administered usually through an intratracheal tube. The operative approach has been made through a long right rectus incision.

OPERATIVE FINDINGS

In a bleeding duodenal ulcer it is surprising how minimal the obvious operative findings are on opening the peritoneal cavity. The presence of blood in the intestine and colon is readily apparent. The anterior duodenal wall and the stomach may appear normal. In none of the cases reported here was it definitely established prior to operation by x-ray examination that the patient had a duodenal ulcer, though in a few of the patients such a diagnosis had been established at an earlier date. As a matter of fact, not uncommonly it is only by efforts directed at separating the medial wall of the duodenum from the pancreas that the presence of a hemorrhagic lesion is established definitely. When the duodenum is opened, by uncovering the perforation the gastroduodenal artery with a slit or a hole in its wall from which blood escapes in jets is visualized at the base of the ulcer crater.

Statistically, a number of studies (Allen,[2] Snell[26]) have determined that a bleeding duodenal ulcer is the most likely cause of massive hemorrhage. If, therefore, the medial wall of the duodenum is applied closely to the adjacent pancreas, the possibility of a small craterous ulcer on the posterior duodenal wall being responsible for the hemorrhage is likely. Such an ulcer may not even be felt and, of course, cannot be seen as long as the duodenum remains in contact with the pancreas. This occurrence, which has come repeatedly now to my attention, suggests that a number of patients who have melena of unlo-

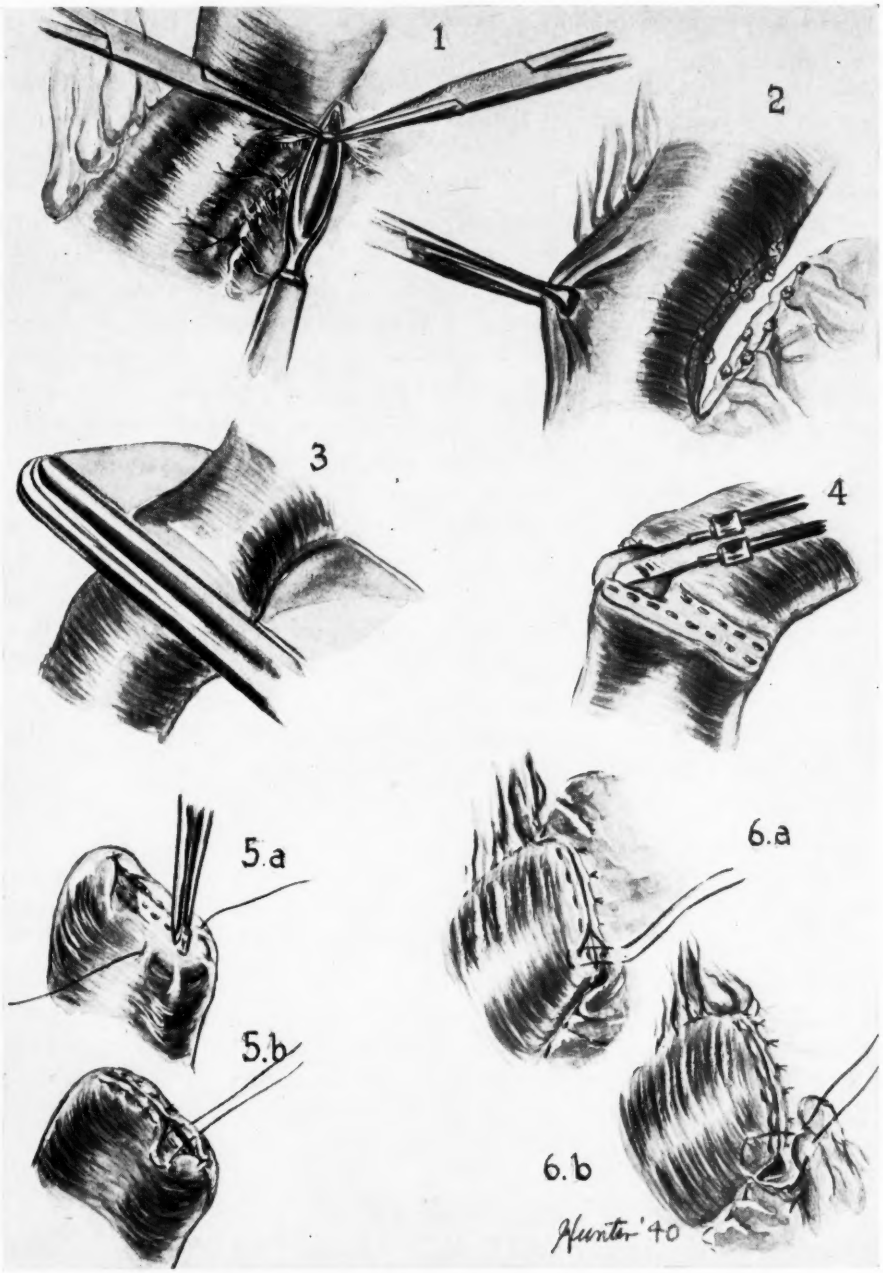

Fig. 1.—Dissection for closure and inversion of duodenum in the Billroth II type of operation. This is the method I employ when the duodenal wall is intact. This method, obviously, is not applicable for duodenal closure when the posterior duodenal wall is perforated.

The attachment between pancreas and medial (posterior) wall of the duodenum is separated as indicated in *1*. The detachment is adequate to permit satisfactory inversion as indicated in *2*. In *3* is shown application of the Petz clamp. Division with the cautery is shown in *4*. *5a* indicates the manner of inverting the duodenal ends and *5b* the closure obtained with a single row of interrupted sutures of fine silk placed after the Halsted mattress pattern. In *6a* is shown the manner of reattaching the pancreatic capsule to the anterior duodenal wall. The manner of placement of sutures at the ends shown in *6b* assures a closed space on the posterior aspect of the duodenal wall.

This method of dissection and suture provides a satisfactory means of securing safe closure of the duodenum.

calized origin may have such an ulcer, which may have escaped detection even by x-ray examination. Such instances have come to my notice. An occult posterior wall duodenal ulcer should be considered in cases of gastrointestinal hemorrhage where the cause remains obscure.

If the posterior duodenal wall is not applied closely to the pancreas and if its wall may be separated from the pancreas with a dissector, it is apparent that it is not the source of bleeding. Whereas induration of the anterior duodenal wall has been present as a concomitant finding in a few of these cases, I have not observed brisk bleeding from an ulcer on the anterior duodenal wall. If examination of the posterior duodenal wall shows it to be removed from immediate contact with the pancreas, search should be extended to the stomach, to the stoma if an antecedent gastroenterostomy has been made, and to a Meckel's diverticulum. I have observed sharp hemorrhage from a gastrojejunal ulcer (Case 7) when no ulcer could be palpated at the stoma from without. In instances in which the stomach cannot be dismissed as a source of bleeding, when other likely origins of the hemorrhage can be excluded reasonably (posterior duodenal wall ulcer and Meckel's diverticulum), an incision transverse to its axis should be made in the body of the stomach. With employment of appropriate deep-bladed retractors, after sponging, the bleeding point will be located if it has its origin within the stomach.

ARREST OF HEMORRHAGE IN DUODENAL ULCER

Having determined by dissection that perforation of the posterior wall of the duodenum onto the pancreas has occurred, the opening in the duodenal wall is extended around the entire circumference of the bowel. This maneuver affords quick exposure of the bleeding point and the objective of the operative procedure; namely, adequate arrest of hemorrhage may be attained within a few minutes after the abdomen is opened. Thereafter, the difficult closure of the duodenal stump and the establishment of a gastrointestinal anastomosis after gastric resection may be undertaken leisurely.

CLOSURE OF THE DUODENAL STUMP

Closure of the blind end of the duodenal stump in the ordinary gastric resection is accomplished easily and is illustrated in Fig. 1. After separating the pancreas adequately from the bowel wall, the duodenum is sectioned between Petz clips with the cautery. A single row of Halsted mattress sutures of fine silk affords usually a satisfactory closure. When, however, the posterior duodenal wall has perforated, satisfactory closure of the duodenum is a most difficult procedure. In the first two patients operated upon in this series, a metal probe was placed in the ampulla of the choledochus while the

bowel wall was being sutured up. One of the deaths in the group (Case 4) was a technical failure, owing to insecure closure of the duodenal stump, with resultant leakage. In this instance the perforation constituted a veritable large granuloma in the medial duodenal wall posteriorly.

When the bleeding vessel has been ligated securely, the posterior duodenal wall is separated adequately from the pancreas to permit closure of the open duodenum as indicated in Fig. 2. This necessitates usually complete excision of the ulcer. In the main it is not possible to mobilize the duodenal wall to secure the type of duodenal wall closure illustrated in Fig. 1. On the contrary, one must be satisfied with burying the closed duodenum in the anterior wall of the pancreas. Attending perforation of the duodenal wall, thickening of the pancreatic capsule occurs, making it practicable to employ it as an additional safeguard to secure effectual closure of the duodenum. This is the only feature of the operation that requires special comment. The technical aspects of the problem are depicted well in the drawing made for me by Mr. Herbert Hunter. In the absence of hemorrhage Finsterer[8] and others who practice extensive gastric resection with antral exclusion for the treatment of duodenal ulcer are content to regard the ulcer in the duodenum, presenting the technical difficulties described here, as irremovable. Finsterer admits freely that the difficulties involved in securing an effectual closure of the duodenum after excision of the ulcer, pyramids the mortality, as contrasted with leaving the ulcer. However, in the presence of active massive hemorrhage there is no choice. In my experience the most satisfactory manner of arresting the bleeding is to open the duodenum as described above, ligating the bleeding vessel or excising the ulcer by placement of sutures. Nissen[22] and Gohrbandt[10] have described closure of the duodenum after excision of "irremovable duodenal ulcer" by techniques very similar to those I have employed.

The operation is completed by excising the antrum and a good portion of the acid-secreting area of the stomach to minimize further trouble from the acid ulcer diathesis. The objective of well-directed surgery in the management of ulcer should be to secure a stomach which empties rapidly and which is achlorhydric to maximal stimulation (histamine). This anastomosis I establish by the closed or aseptic method, the details of which have been described previously (Fig. 3). Unless a gastroenterostomy has been made previously, delimiting the proximal extent of the resection, an attempt should be made to excise a generous segment of the corporic and fundic zones to insure effectual reduction of gastric acidity. After the hemorrhage has been satisfactorily controlled, such adequate excision of gastric tissue adds but little to the risk, but has important significance for the ultimate results.

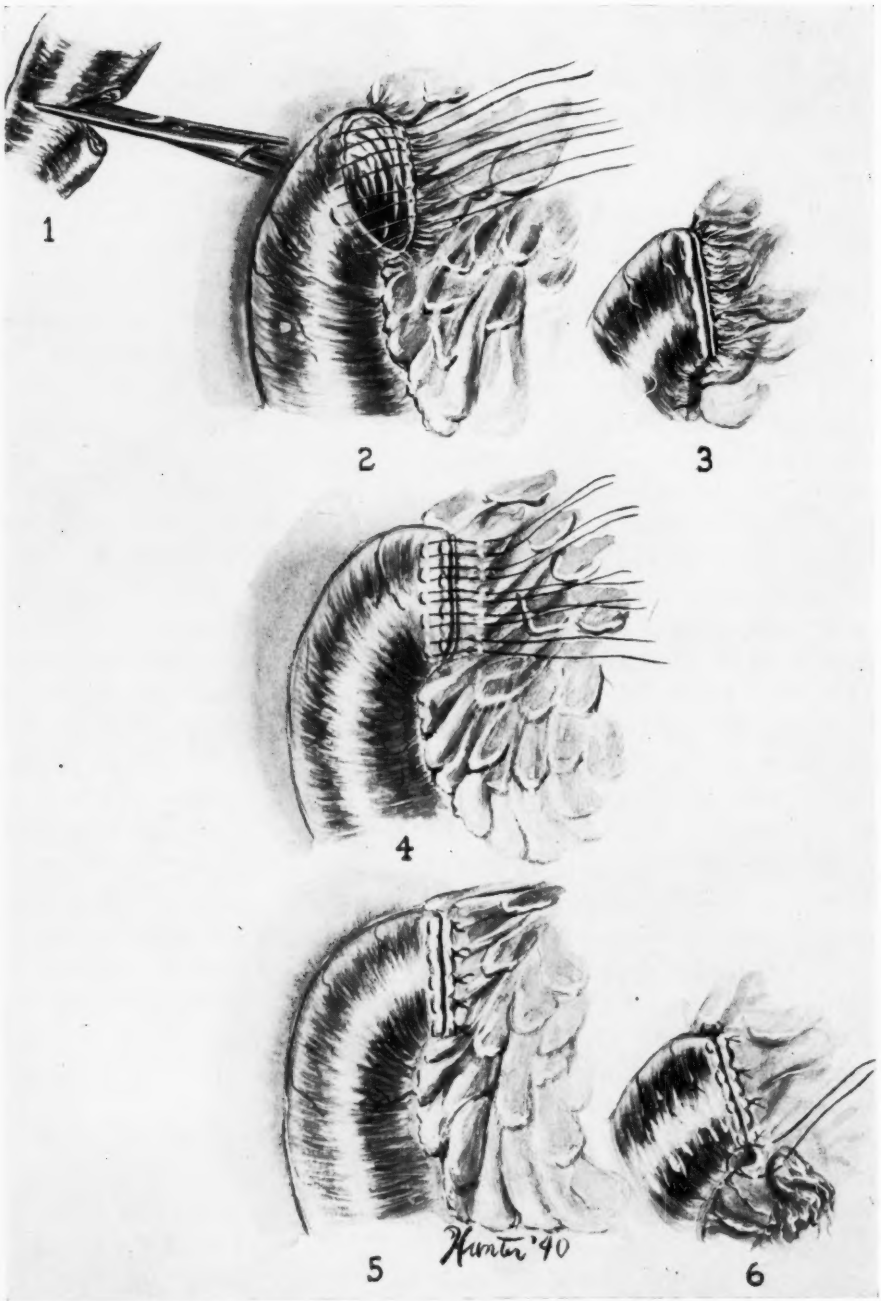

Fig. 2.—Method of closure of duodenum in massive hemorrhage causing shock and necessitating emergency operation for arrest of bleeding. Such an ulcer presents invariably perforation on the posterior duodenal wall and the technique depicted in Fig. 1 cannot be employed.

The dissection and separation of the medial (posterior) duodenal wall from the pancreas is begun as shown in the first step in Fig. 1. This dissection succeeds in disclosing a perforation in the posterior duodenal wall in massive hemorrhage. The anterior duodenal wall is then cut across totally with scissors as indicated in *1* and the bleeding vessel is ligated.

In *2* is shown the placement of interrupted Halsted mattress sutures of fine silk across the open end of the duodenum. None are tied till all are placed. The duodenal walls are approximated as shown in *3* when the sutures are tied. This closure is by no means as satisfactory as that shown in *5a* and *5b* in Fig. 1, employed when the duodenal wall is not perforated. However, when reinforced as shown in *4*, *5*, and *6* there by burying the closed duodenal end in the pancreatic capsule, a satisfactory closure usually can be obtained even in difficult cases. Particular note is to be taken of the manner of insuring a closed space on the posterior duodenal wall (*6*). This is a *most* important item in the procedure. Such a suture is placed at the upper end as well.

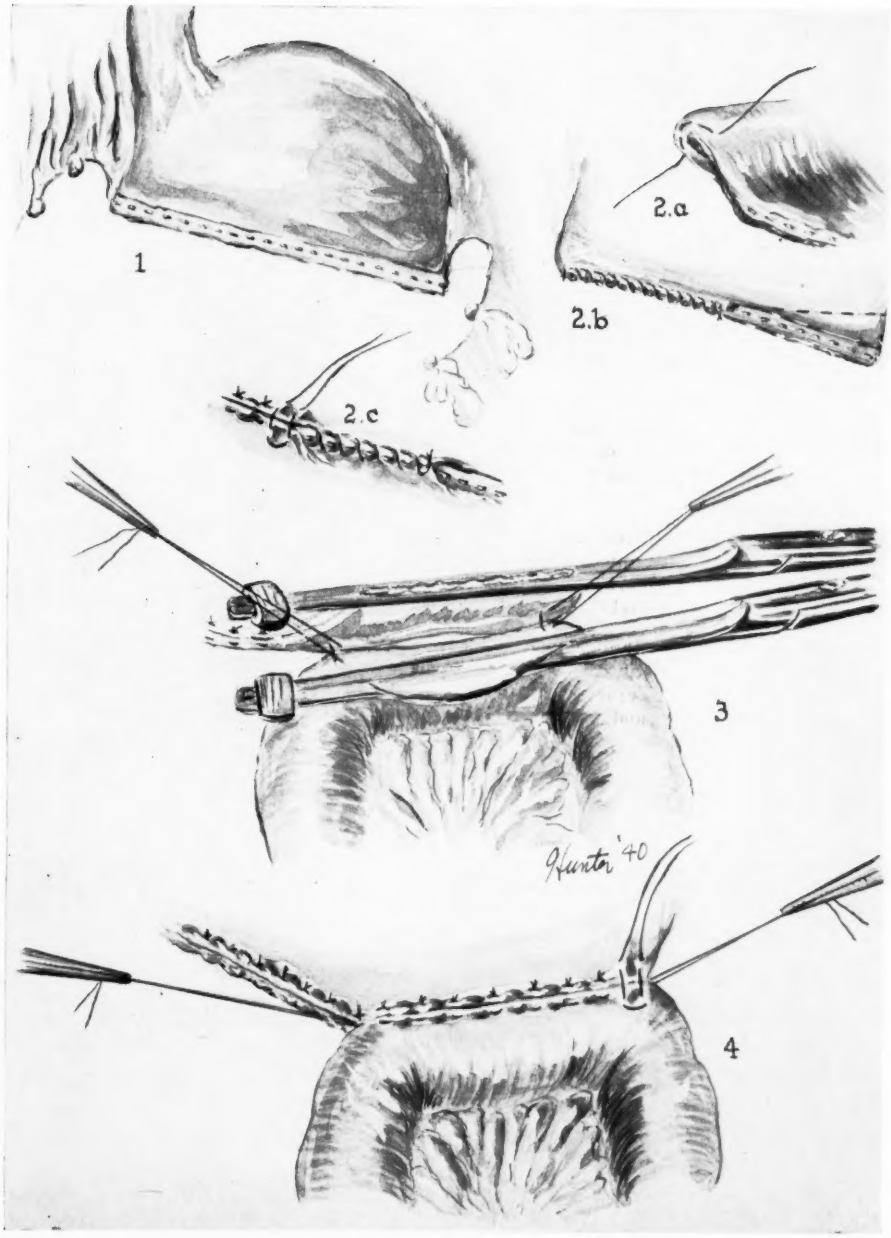

Fig. 3.—Aseptic gastric resection, method of establishing gastrointestinal continuity. The aseptic or closed method was employed in all the cases listed herein (Table I). In the first six cases excision of the pylorus and antrum only was done (complete terminolateral anastomosis [Polya]) without enteroanastomosis. In Case 7 the excision was of the extent shown here and an incomplete (inferior) terminolateral (Hofmeister) anastomosis with enteroanastomosis was made, the type of excision and anastomosis carried out as an elective procedure for complicated ulcer when the Billroth II method is employed. Achlorhydria even to maximal stimulation with histamine follows this extent of excision of gastric tissue usually; achlorhydria attends antral excision rarely.

In *1* is shown the site of amputation of the stomach and the clips deposited by the Petz suturing apparatus. *2a* indicates the manner of inversion of the dog ear at the upper end. The dotted line at the lower end of the stomach in *2b* indicates the site at which the anastomosis will be established. This small segment of stomach is removed with the cautery after satisfactory hemostasis has been attained by a running suture of catgut over the Petz clips where the stomach is inverted above. The inversion is obtained with a single row of fine silk sutures placed after the Halsted mattress pattern (*2c*).

In *3* is indicated the manner in which the anastomosis (6 cm. in length) is established by the closed or aseptic method. It is to be noted that the portion of the jejunum engaged in the clamp is not cut off until the posterior row of sutures has been placed. In *4* the completed anastomosis is shown. The details of this technique have been described previously.

TABLE I

OPERATIONS FOR MASSIVE HEMOR

CASE NO. NAME HOSPITAL NO. AGE	OPERATIVE DIAGNOSIS	DURATION OF BLEEDING	PREVIOUS OPERATIVE PROCEDURE	OPERATION*— DATE, PROCEDURE, SIZE OF RESECTION	DURATION OF OPERATION
1. Mr. C. M. No. 623906 49 yr.	Perforated posterior wall duodenal ulcer with erosion of gastroduodenal artery	96 hr.	11/14/38 gastroenterostomy for bleeding	12/17/38 gastric resection	1 hr. 50 min.
2. Mr. L. K. No. 669044 24 yr.	Perforated posterior wall duodenal ulcer with erosion of gastroduodenal artery	24 days	2/14/39 gastroenterostomy for bleeding	2/21/39 gastric resection	1 hr. 55 min.
				5/15/39 Schmilinsky operation	2 hr. 40 min.
3. Mr. L. W. No. 643715 52 yr.	Perforated posterior wall duodenal ulcer with erosion of gastroduodenal artery	23 days		9/3/39 gastric resection	2 hr. 35 min.
4. Mr. G. C. No. 611604 36 yr.	Perforated posterior wall duodenal ulcer with erosion of gastroduodenal artery	11 days		9/17/39 gastric resection	2 hr. 50 min.
5. Mr. J. K. No. 669010 80 yr.	Perforated posterior wall duodenal ulcer with erosion of gastroduodenal artery	20 days	None	9/17/39 gastric resection	2 hr. 45 min.
6. Mr. G. A. No. 661081 58 yr.	Perforated posterior wall duodenal ulcer with erosion of branches of gastroduodenal artery	8 days	None	9/18/39 gastric resection	2 hr. 55 min.
7. Mrs. E. F. No. 693430 57 yr.	Duodenal ulcer with obstruction, with bleeding gastrojejunal ulcer	17 days	20 yr. ago gastroenterostomy	4/13/40 gastric resection	3 hr. 30 min.

*All gastric resections in the group are antral resections (pylorus and antrum) except Case 7, in which 75 per cent of the total square area was excised. Enteroanastomosis was done in Case 7 only. Save for the patient in Case 3, who has occasionally been achlorhydric, only one of the survivors (Case 7) has been persistently achlorhydric to stimulation with histamine.

†All the survivors have reported for examination on several occasions since this was written. All are subjectively and objectively well.

In my experience the removal of 200 sq. cm. of gastric tissue (measured on the peritoneal surface) with a Polya type of anastomosis insures quite uniformly effectual reduction of gastric acidity. Scott found the average total square area of the gastric mucosa in six adult stomachs to be 525 sq. cm. Scott's measurements, however, took into account the rugation of the mucous folds. It is apparent, therefore, that more than 200 sq. cm. of gastric mucosa is sacrificed actually in the excision of gastric tissue described above. On the basis of a larger number of gastric resections done for other varieties of ulcer,

I

RHAGE FROM DUODENAL ULCER*

IMMEDIATE RESULTS	ULTIMATE RESULTS†	AMOUNT OF BLOOD TRANSFUSED	LABORATORY	BLOOD PRESSURE (LOWEST JUST BEFORE OPERATION)	PULSE (HIGHEST JUST BEFORE OPERATION)
Recovered	2/26/40 well	1,100 c.c. before operation; 1,700 c.c. during operation; 300 c.c. after operation	Hb. 38 R.B.C. 2,500,000	76/58 shock	110
Recovered Recovered	9/16/39 died from perforated jejunal ulcer	3,500 c.c. before first; 4,750 c.c. before second, 500 c.c. after second, 1,500 c.c. after third operation	Hb. 32 R.B.C. 2,170,000	0/0 shock	Not palpable
Recovered	4/22/40 well	2,200 c.c.	Hb. 42 R.B.C. 2,480,000	82/54 shock	112
9/19/39 died, peritonitis		4,000 c.c.	Hb. 47 R.B.C. 3,500,000	68/32 shock	122
Died 8 hr. after operation		500 c.c.	Hb. 55 R.B.C. 2,850,000	74/50 shock	120 irregular
Recovered	4/23/40 well	1,000 c.c. before operation; 500 c.c. during operation; 500 c.c. right after operation; 1,500 c.c. after operation	Hb. 39 R.B.C. 2,400,000	120/82 No shock	108
Recovered	4/25/40 discharged, well	9,600 c.c., including 2,600 c.c. before and after operation (7,000 c.c. at Miller Hospital, St. Paul)	Hb. 30	64/32 shock	136

I estimate that it is necessary to sacrifice two-thirds to four-fifths (66 to 80 per cent) of the total gastric area (in an unobstructed stomach of average size) to remove 200 sq. cm. measured as indicated above. Such resection, when accompanied by a gastrojejunal anastomosis, affords a stomach which is achlorhydric usually even to maximal stimulation. Similar extensive gastric resection, unaccompanied by gastrojejunostomy, fails to make the stomach achlorhydric.[28, 29]

It is becoming recognized more generally that gastrointestinal surgery is a highly specialized variety of operative procedure. The two Mayos, to whom these pages are dedicated, established an enviable record in the management of gastric lesions. Balfour's accomplish-

ment with difficult gastric operations attests the importance of concentrating this type of surgery in the hands of a few persons in every surgical clinic.

IMPORTANCE OF ADEQUATE ARREST OF HEMORRHAGE

In Allen and Benedict's first group of fatal cases from massive hemorrhage, there were 28 patients. Twenty died under conservative management; 8 died after surgery; of these 8 cases, all but 1 died of hemorrhage. Ligature of the gastroduodenal and the right gastroepiploic arteries does not suffice to control hemorrhage. Bleeding may still occur through the open vessel in the base of the ulcer, via the inferior pancreaticoduodenal artery, a branch of the superior mesenteric.

In the present group there were 2 deaths. Neither died of hemorrhage. One (Case 4), aged 36 years, died two days after operation because of inadequate closure of the duodenal stump. The other, a man 80 years of age (Case 5), died eight hours after operation. His condition on the completion of the operation was better than at the beginning. I declined to operate because of the patient's age and poor condition twenty-four hours earlier and intervened in time to accept the lethal issue as a surgical death. Granted that the bleeding is arrested effectually, these patients, in the main, stand prolonged operation well (see Table I for time and length of operation). In all the patients listed here, operation was undertaken as an emergency operation for the control of hemorrhage. In most instances the operation could reasonably have been described as an ante-mortem operation.

My experience in the control of massive hemorrhage is outlined in Table I. There were 2 deaths among 7 cases, a mortality of 28.5 per cent.* The records of the hospital indicate that in 8 other instances, dating back to 1921 when the first case was done, operation has been undertaken for the control of active hemorrhage of ulcer origin. Three of the 8 died, a mortality in this latter group of 37.5 per cent. These operations, however, were largely indirect procedures.

SUMMARY

Massive hemorrhage is a not uncommon cause of death in duodenal ulcer. Approximately 10 per cent of patients treated conservatively for massive hemorrhage of ulcer origin die. The lives of a number of such patients may be salvaged by timely surgical intervention. The recovery of 5 of 7 patients subjected to ante-mortem operation for the control of hemorrhage suggests, in the main, that such patients stand

*Since this paper was written, three additional patients exhibiting massive hemorrhage from duodenal ulcer have been operated upon after the plan outlined in Fig. 3. All three recovered and have been observed in the out-patient clinic, and all are achlorhydric to histamine stimulation. (Mr. W. W., U.H. No. 647102, aged 67 years; Mr. P. S., U.H. No. 695376, aged 59 years; and Mr. L. A., U.H. No. 677349, aged 26 years.) The mortality in this group up to date, therefore, is 10 per cent.

operation tolerably well if the bleeding is adequately controlled. A means of uncovering the bleeding point, dealing with the open vessel, and a manner of securing satisfactory closure of the duodenum are described.

It is pointed out that fall of blood pressure to a shock level, necessitating transfusion of large quantities of blood to maintain the blood pressure at 100 mm. Hg, suggests that the patient has an open vessel. In massive hemorrhage from duodenal ulcer the gastroduodenal artery is eroded, owing to perforation of the posterior duodenal wall. The ulcer itself is often occult, presenting usually even at operation during active hemorrhage no tangible signs until the perforation is uncovered. Patients with duodenal ulcer who bleed slowly to low levels of hemoglobin (20 to 40) without manifesting significant falls in blood pressure do not exhibit complete perforation of the duodenal wall nor do they have a hole in a large vessel, but present usually erosion of small vessels within the bowel wall.

The most difficult question to decide is when operation should be undertaken. No one can say in which patients bleeding will cease automatically. The longer the bleeding period before operation, the more serious is the risk. The patient with massive hemorrhage who bleeds to shock level, in whom it is difficult to maintain a satisfactory blood pressure, should be submitted to immediate operation, as soon as blood loss is replaced adequately. In other patients Finsterer's dictum of waiting forty-eight hours to determine whether bleeding will cease spontaneously is sound advice. However, until the hazards of massive hemorrhage become known more generally, it is not likely that patients with threatening hemorrhage will come to operation early.

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THE USE OF THE MILLER-ABBOTT TUBE IN THE SURGERY OF THE LARGE BOWEL

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DURING the past decade one of the most remarkable advances in surgical therapy has occurred in the treatment of the ever-dreaded lesion of acute ileus. In 1918 the mortality in this condition, in three of the leading university clinics of this country, was 66 per cent. Following the better understanding of fluid and electrolyte imbalance,[1] so striking in cases of high intestinal obstruction, and the application of this knowledge in restoring this balance before operation, the mortality showed an amazing decrease. In the Presbyterian Hospital in New York City the mortality dropped from the figure of 66 per cent in the 1919 to 1924 period to 29.6 per cent in the 1932 to 1937 period.[2] This improvement was due chiefly to restoration of fluid and salt balance, but a considerable credit was also due to the use of continuous duodenal suction, before and after operation, by the method popularized by Wangensteen's[3] classic work.

Following extensive experimental studies in intestinal intubation by Miller and Abbott[4] and their associates, Abbott applied the technique to the management of clinical cases of intestinal obstruction. The first sixteen cases so treated were reported by Abbott and Johnston[5] in 1938. Abbott,[6] in Philadelphia, and Johnston[7] and his co-workers, in Detroit, have continued the work in a large number of cases with amazing success.

Following Abbott's first report, we became convinced of the possibilities of this method in treating acute ileus and in 1938 we assigned two of our residents to this study. After observing the technique by Abbott, in Philadelphia, Leigh and Nelson of our surgical staff and Swenson of our roentgenological staff studied every case of acute ileus, mechanical and paralytic, in the Presbyterian Hospital. In 1939 we assigned one of our head nurses, Miss Stines, to the care of these patients as regards the detailed management and care of the tubes, and she has worked with the residents in this important field.

Our results in cases of acute ileus, using the Miller-Abbott intubation, have been so dramatic that we hesitated to report them; but, following almost equally striking results by Johnston and his associates in Detroit, Leigh, Nelson and Swenson[8] reported our results in February of this year. The summary of this report is taken from their paper and is given in Table I. In addition to intubation these patients all had

analyses of their blood structure and fluid and salt balance restoration, which accounts for some of the remarkable improvement in the mortality of acute ileus.

It is important to emphasize the fact that this method of intestinal intubation carries with it tremendous possibilities for good as well as danger to the patient, depending upon the thorough understanding of these possibilities and the intelligent and diligent application of the technique of the method. The reason that so many hospitals have failed to appreciate the value of the Miller-Abbott tube in dealing with cases of ileus is that no one person has learned the application and technique of the method and acquired the experience necessary to its success. The reader is referred to the paper by Leigh, Nelson, and Swenson[8] for a detailed discussion of the proper use of the tube in intubating the intestine.

TABLE I

SUMMARY OF CASES OF SMALL INTESTINAL OBSTRUCTION TREATED WITH MILLER-ABBOTT TUBE AND SURGERY

TYPE OF OBSTRUCTION	NO. OF CASES	OPERATIONS FOR ILEUS	DIED	MORTALITY
Noninflammatory obstructions	50*	27	1	2.0%
Paralytic type	12	1	0	0
Mechanical type	38	26	1	2.7%
Obstructions with peritonitis	21	10	7	33.3%
Tube passed into small bowel	14	2	1	7.1%
Tube *failed* to pass into small bowel	7	8†	6	85.7%
Obstructions with gangrene of bowel	5	6†	2	40.0%
Total cases with obstruction	76	43	10	13.2%
Total cases with tube passing into small bowel	68	35	4	5.9%

*One case discontinued. Patient hysterical.
†Two cases required two operations for ileus.

As these studies in acute ileus progressed, we appreciated the possibilities of using the Miller-Abbott tube as a preoperative measure to prevent distention and vomiting after intestinal resection. In peritonitis cases we had learned of the possibilities of feeding patients wearing the tube and the possibilities of restoring protein and vitamin loss in depleted patients. We believe the most important single factor in the success of intestinal anastomosis is to avoid distention of the anastomosed segment. Distention favors tension on the suture line and diminishes the blood supply in the gut wall, resulting in devitalization of the tissues included in the sutures, separation of agglutinated edges, leakage of gas and intestinal contents, with peritonitis or at best a fistula with localized peritonitis. For small intestinal anastomosis and for one-stage right-sided colectomy with ileocolostomy the advantages of a collapsed normal bowel before and after operation were obvious, and our results with the pre- and postoperative use of the tube clearly corroborated

TABLE II

MORTALITY OF RESECTIONS OF LARGE BOWEL (112 CONSECUTIVE CASES—1938-1940)*

	WITHOUT MILLER-ABBOTT TUBE			MILLER-ABBOTT TUBE USED IN PRE- AND POSTOPERATIVE PERIODS			TOTALS		
	RESECTIONS	DEATHS	MORTALITY	RESECTIONS	DEATHS	MORTALITY	RESECTIONS	DEATHS	MORTALITY
Right colon, one stage	7	1	14.3%	15	0	0	22	1	4.5%
Left colon, one stage	15	3	20.0%	5	0	0	20	3	15.0%
Left colon, obstructive resections	18	4	22.2%	5	1	20.0%	23	5	21.0%
Rectosigmoid, one-stage abdominoperineal resections	28	4	14.3%	11	0	0	39	4	10.3%
Rectosigmoid, two stage	8	2	25.0%	0	0	0	8	2	25.0%
Totals	76	14	18.4%	36	1	2.8%	112	15	13.4%

*Thirty-six cases with one death where Miller-Abbott tube was passed preoperatively and used postoperatively until normal bowel function was established. One death due to a lung abscess following a pulmonary infarction. No postoperative distention. Tube out second postoperative day, infarction eighth postoperative day, death twenty-first postoperative day.

this premise. When we tried the tube in cases of left-sided colectomy and abdominoperineal resections of the pelvic colon and rectum, we found that the results were not so striking. In fact cecostomy as a preliminary measure in these cases where mechanical obstruction was complete or nearly so is still clearly indicated, because the tube does not pass the ileocecal valve in a distended cecum, and the additional pre- and postoperative use of the tube helps only in preventing postoperative ileus and distention of the small intestine, a very great boon in many of these cases, as regards their freedom from distention, vomiting, and tension on the abdominal wound.

TABLE III

CAUSES OF DEATH (112 CONSECUTIVE RESECTIONS OF LARGE BOWEL—1938-1940)*

	RIGHT COLON	LEFT COLON		ABD.-PER. RESECTIONS		TOTALS
	ONE STAGE	ONE STAGE	OBSTRUCTIVE RESECTIONS	ONE STAGE	TWO STAGE	
Directly related to operative procedure						
Peritonitis	1	1	1	0	2	5
Intestinal obstruction	0	1	0	2	0	3
Hemorrhage from perineal wound	0	0	0	1	0	1
Indirectly related to operative procedure						
Pneumonia	0	1	2	0	0	3
Hemophilia—hemorrhage	0	0	1	0	0	1
Lung abscess	0	0	1	0	0	1
Cerebral hemorrhage	0	0	0	1	0	1
Totals	1	3	5	4	2	15

*Peritonitis was always complicated by intestinal obstruction. Early peritonitis only in cases with abscess at operation. Late peritonitis followed wound infections or leakage of anastomosis.

We are reporting 112 consecutive unselected cases operated upon by our surgical staff during the years 1938-1940. Tables II and III give the results in the surgery of several parts of the colon (including rectum) with the one- and two-stage resections and the obstructive resections (Rankin operation), with and without the pre- and postoperative use of the Miller-Abbott tube and the total cases. The figures speak for themselves. We, at least, are convinced from the observation of our patients that the pre- and postoperative use of the tube in the surgery of the colon is not only a lifesaving measure, but one that adds greatly to the comfort and smooth convalescence of the patients undergoing this hazardous type of surgery.

We must again emphasize the absolute necessity of having some one member or members of the surgical staff learn the technique and management of intestinal intubation if it is to be used to treat or prevent

intestinal obstruction or distention, and again urge the careful reading of the previous communication from this clinic by Leigh, Nelson, and Swenson.[8]

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REGIONAL LYMPHATIC METASTASIS OF CARCINOMA OF THE RECTUM*

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A KNOWLEDGE of the lymphatic spread of carcinoma from primary lesions of the rectum is essential in the treatment of that disease. The normal lymphatic drainage of the rectum and rectosigmoid colon is well known, but it is often impossible to decide before operation whether metastasis has occurred or not. Consequently, we have no method of determining with certainty the operability and prognosis of any given carcinoma of the rectum.

The aim of the surgical treatment of carcinoma of the rectum is cure. The surgical procedure directed toward the removal of the primary tumor alone is of little value, other than perhaps temporary palliation. To effect a cure, both the primary neoplasm and its metastases must be excised. This is impossible in cases of hematogenous metastasis, but the regional lymph node metastasis frequently is amenable to operative removal.

This study, similar to one made by Gilchrist and David,[1] is based on the dissection and examination of all the lymph nodes from 53 carcinomas of the rectum. Of these, 48 were removed by combined abdominal-perineal resection, one by perineal resection, and four were autopsy specimens. The lymph nodes were dissected from each specimen after they had been visualized (Fig. 1) by clearing by the Spalteholtz method as modified by Gilchrist and David. All nodes were examined individually and the results charted on previously prepared outline drawings upon which each node was indicated. These findings were then correlated with (1) the age of the patient, (2) duration of symptoms, (3) gross type of lesion, (4) location above the mucocutaneous junction, (5) site of origin of the neoplasm, (6) size, (7) amount of circumference of the bowel wall involved, (8) depth of infiltration, (9) microscopic type, (10) degree of cellular differentiation, and (11) the presence of associated precancerous lesions, such as polypi and ulcerative colitis.

Regional lymph nodes may thus be isolated which, because of their smallness, go unnoticed by the usual method of dissection. Specimens have been examined in which there were no nodes palpable but which, upon clearing, were found to include lymph nodes as small as 1 to 2 mm. in diameter, containing nests of metastatic carcinoma (Fig. 2). No correlation existed between the size of the lymph nodes and the

*This study was aided by the James and Elizabeth Inglis Fund for Surgery Research.

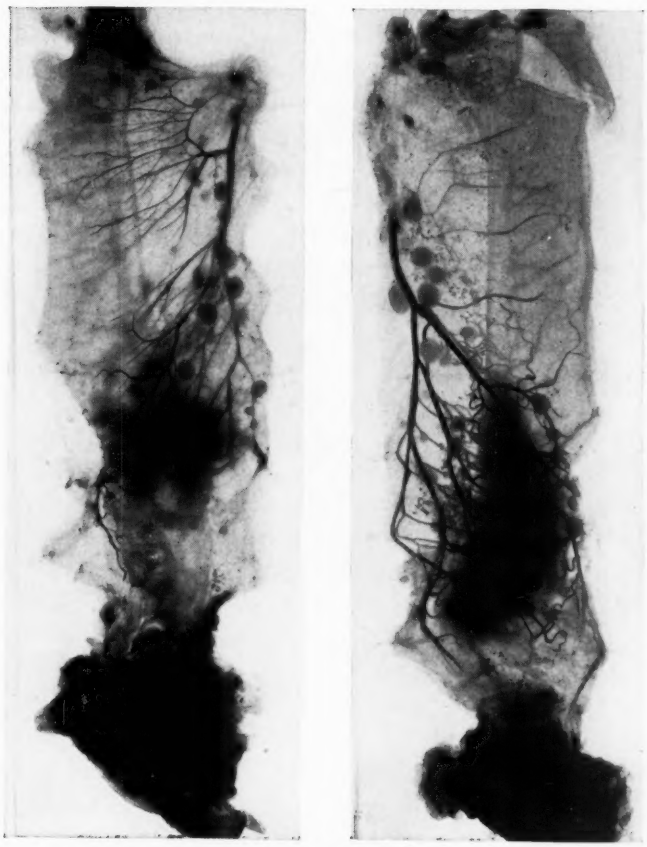

Fig. 1.—Photographs of cleared specimens of carcinomas of the rectum.

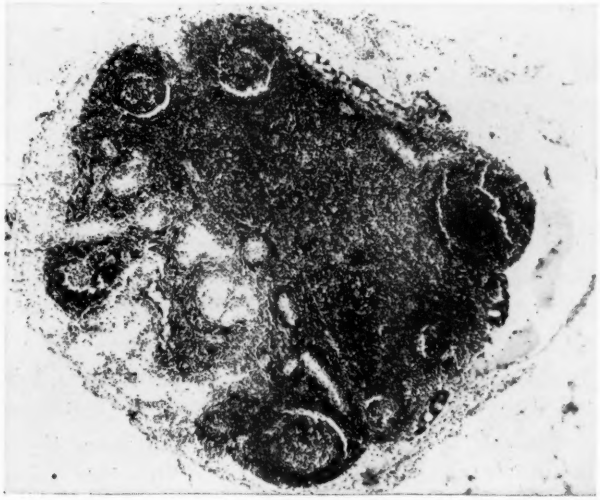

Fig. 2.—Photomicrograph of a lymph node only 1.5 mm. in diameter, showing metastatic carcinoma in the subcapsular lymph channels.

presence in them of metastases. Many large nodes were inflammatory and many small impalpable nodes contained neoplasm.

For comparison we studied a similar group of cases treated in 1934 and 1935. These specimens were examined by gross manual dissection and an average of only 3.5 lymph nodes per specimen were found. The largest number of nodes found by this method in any one specimen was 12, and 25 out of 46 cases (54 per cent) were reported as being free from metastases. In the present study as many as 194 lymph nodes have been isolated from a single operative specimen, and an average of 67 per specimen was found. With this more accurate method of study, the number of cases showing no involvement of the lymph nodes has decreased to 35.8 per cent. In other words, 64.2 per cent of the cases examined had metastases in the regional lymph nodes. This finding is similar to that of Gilchrist and David who found 68 per cent of the specimens to have metastases in the lymph nodes.

Regional lymph node metastasis is only one factor in determining the operability and prognosis in carcinoma of the rectum. Inoperability or poor prognosis may result from extensive local infiltration, hematogenous metastases, or peritoneal implants. In the most favorable of our cases, those in which radical operation was performed, 15 per cent showed microscopic evidence of infiltration into blood vessels. The hematogenous spread of carcinoma is an unpredictable factor. In one of our cases symptoms of occasional rectal bleeding had been present for only one month. The neoplasm, measuring only 2 cm. in diameter, had infiltrated just to the muscle layer and was a moderately well-differentiated adenocarcinoma mucosum of Grade II malignancy. Judged by clinical criteria, this patient had a good prognosis, but microscopic examination showed invasion of both lymph and blood vessels. The degree of malignancy was not a determining factor in the occurrence of hematogenous metastases, for, of the specimens in which metastasis was found microscopically, six lesions were Grade II, one was Grade IV, and one a spindle-cell sarcoma. Two of these had invasion of the blood vessels but no lymphogenous metastases.

According to the classic description of the lymphatic spread of carcinoma of the rectum by Miles[2, 8] and the anatomic description of the lymphatic system of the rectum and anus by Delamere, Poirier, and Cuneo,[3] three collecting systems are present, the superior, lateral, and inferior routes of lymphatic drainage corresponding to the superior, middle, and inferior hemorrhoidal veins and classified by Miles as the extramural lymphatics into which the intramural and intermediary systems drain. The intramural lymphatics consist of two freely communicating networks located within the wall: one, the submucosal, and the other, the intermuscular network. These intercommunicate by radial lymph channels lying between the circular muscle fibers. The submucosal network is to a lesser extent continuous, above, with the pelvic colon, and below, with the subcutaneous lymph channels of the

perianal skin. The tendency of carcinoma to spread through the submucosal network (Fig. 3*A*) does not appear to be as common as to spread by the radial channels into the deeper intermuscular network (Fig. 3*B*). The intermuscular network lying between the circular and longitudinal muscle coats communicates with similar channels of the pelvic colon above, and below with those of the external sphincter

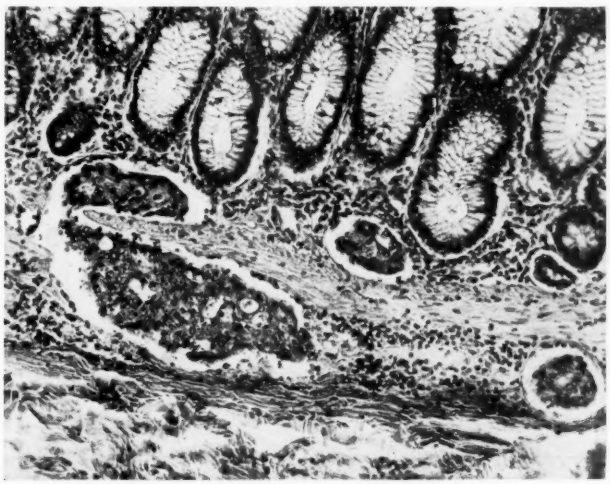

Fig. 3*A*.—Photomicrograph of submucosal lymph channels showing neoplastic emboli.

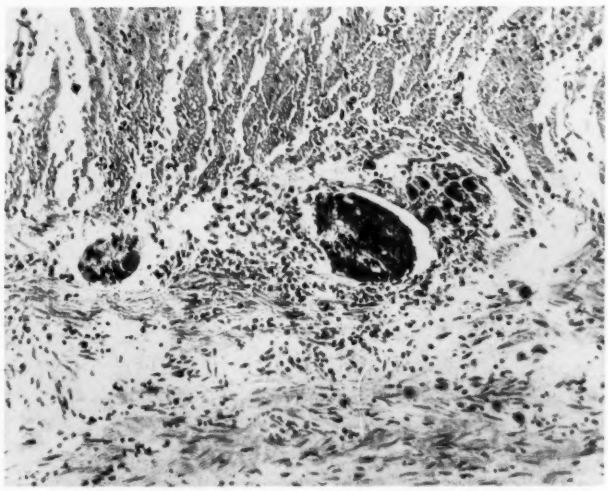

Fig. 3*B*.—Photomicrograph demonstrating neoplastic emboli in the intermuscular lymphatic network.

muscles. The main avenue of dissemination, however, is through the external muscle coat to the intermediary system, which consists of two parts, a subserous network in that portion of the rectum invested with a peritoneal covering, and a lymph sinus, situated between the external muscular coat and the perirectal fat in that part of the rectum beneath the peritoneal reflection.

The third lymphatic system, and the one which is most important surgically, is the extramural. The efferent channels from the lymph sinuses and subserous lymph channels form an extensive plexus which drains into the anorectal glands of Gerota which are scattered over the lateral and posterior aspects of the rectum and lie in the hollow of the sacrum. The efferents of these drain into the lymph channels accompanying the superior hemorrhoidal vein (the superior zone of spread) (Fig. 3*C*), into the middle hemorrhoidal vein (the lateral zone of spread), or if the lesion is low enough, into the lymph channels accompanying the inferior hemorrhoidal vein (the inferior zone of spread). Cancer cells thus may metastasize in any one of the three zones of spread, upward, laterally, or downward. There are many cases showing evidence of metastases in more than one zone of spread, this being especially true of carcinoma of the anal canal. Spread by the inferior zone may occur along the subcutaneous perianal lymph channels in the perineum to the inguinal lymph nodes or through the ischiorectal fossa, Alcock's canal, and into the internal iliac lymph nodes. In untreated cases and in those which have recurrences, it is not uncommon to find carcinomatous nodules in the perineum, rectovaginal septum, and ischiorectal fossa. Consequently, operative removal should include wide excision of the perianal skin, ischiorectal adipose tissue, and levator ani muscles.

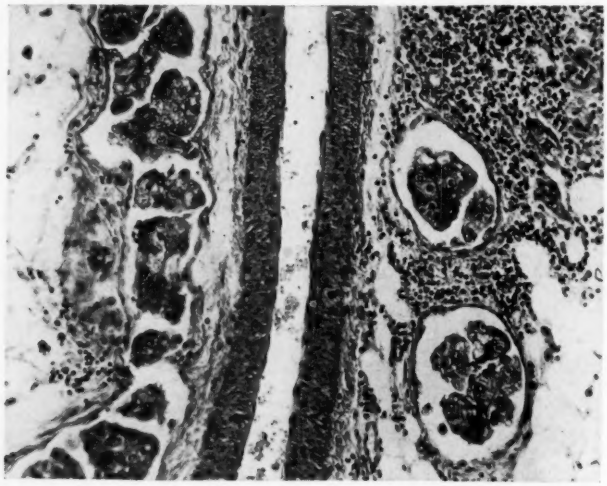

Fig. 3*C*.—Photomicrograph demonstrating neoplastic emboli in the extramural collecting system accompanying a large blood vessel.

The lateral efferent lymphatics drain into a number of channels accompanying the middle hemorrhoidal vessels and lie between the pelvic peritoneum, endopelvic fascia, and levator ani muscles. These also eventually drain to the lymph nodes along the internal iliac veins. This route of spread was beautifully demonstrated by an autopsy case in which retroperitoneal dissection of the entire contents of the lower abdominal, pelvic, and inguinal regions was made (Fig. 4).

The upward zone of spread is along the lymph channels and nodes in the retrorectal and retrocolic position accompanying the superior hemorrhoidal vessels along the base of the sigmoid mesocolon and continuing with the inferior mesenteric vessels.

Lymphatic vessels differ from the blood vessels in that, instead of one or two channels draining the same area, the lymph is returned by several channels which tend to form a plexus about the blood vessels. There may also be a number of efferent vessels to any one node, thus explaining the observation that contiguous lymph nodes are not necessarily involved and that the nodes at various levels may be implicated. Lymph nodes act as barriers to filter out neoplastic emboli. A neoplastic embolus enters a lymph node by its peri- and subcapsular lymph channels (Fig. 2). If the metastasis remains viable, it sets up a new neoplastic focus, tending to block the lymph channel, which then

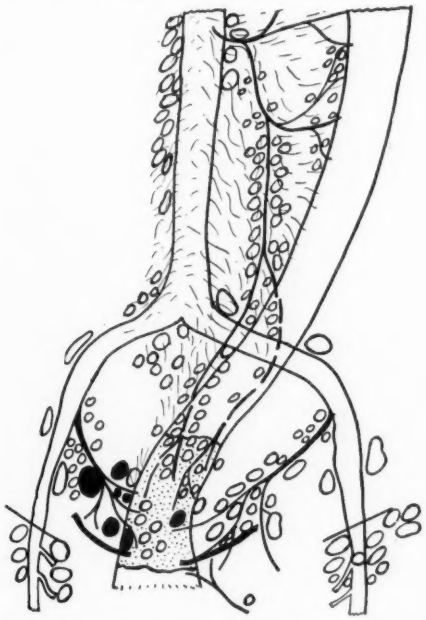

Fig. 4.—Line drawing of an autopsy specimen illustrating the lateral zone of lymphatic spread from an adenocarcinoma, Grade II, of the anal canal; 170 lymph nodes isolated, 7 of which, lying along the right middle hemorrhoidal artery, are replaced by metastatic carcinoma.

becomes dilated and distended with lymphocytes. Lymph flow becomes static and other neoplastic foci may be established along the lymph channels. It is therefore common to find multiple small neoplastic nodules in the perirectal adipose tissue. The direction of lymphatic metastases depends on the direction of the lymph flow, and, if it becomes obstructed by neoplastic emboli, the lymph will then find unobstructed channels. Not until there have been extensive metastases along the superior zone of spread do all or a majority of the lymph channels become sufficiently obstructed to cause a retrograde flow of lymph. In our cases, even in those with extensive metastases, we had no evidence

of retrograde metastases to nodes situated a significant distance below the primary site, in contradistinction to the four cases reported by Gilchrist and David. In seventy-four cases studied by Westhus[4] there was evidence in only one instance of retrograde metastasis. This undoubtedly does occur, but it must be exceedingly rare.

From a surgical viewpoint, the extramural lymphatics are of more importance than the intramural. An understanding of the intramural lymph channels, however, is important in order to realize how superficial malignancies involving only the submucosa and muscular layers may metastasize.

AGE AND LYMPH NODE METASTASIS

The average age was 53.3 years in those with metastases and 53.5 years in those without. In analyzing the cases by decades (Table I) there was no significant variation found. Grouping the cases into those below and those above 50 years of age, it was found that 70 per cent in the younger age group had metastases in comparison to 60.6 per cent in the older. The only carcinoma of histologic Grade IV was in the 20- to 30-year age group.

TABLE I

CORRELATION OF DECADE OF LIFE AND METASTASES

DECADE	NUMBER OF CASES	WITHOUT METASTASES		WITH METASTASES	
		NUMBER OF CASES	PERCENTAGE	NUMBER OF CASES	PERCENTAGE
20–30	2	0	0	2	100
30–40	6	3	50	3	50
40–50	12	3	25	9	75
Totals	20			14	70
50–60	14	7	50	7	50
60–70	17	5	29.4	12	70.6
70–80	2	1	50	1	50
Totals	33			20	60.6

In a correlation of age and degree of malignancy in carcinoma of the colon by Rankin and Broders,[5] it was reported that carcinoma in younger age groups tended to be of a higher grade of malignancy than in the group as a whole, and because of this there was a greater tendency to metastasize. This is undoubtedly true, but there are other factors present in younger individuals which also influence the tendency of neoplasms to metastasize. Fascial planes and connective tissue are known to act as a barrier to the advancing malignancy. Lymph and blood vessels in elderly people are thickened by deposition of connective tissue in their walls, thus presenting more of a barrier to infiltration.

DURATION OF SYMPTOMS AND METASTASES

No relation existed between duration of symptoms and the occurrence of metastases. There was an average duration of symptoms

of 8.42 months in the cases in which metastases had occurred, and 9.44 months in the group in which metastases had not occurred. This illustrates the point that the case with the shortest history is not always the most favorable for treatment. There were three patients in the series with symptoms of rectal carcinoma for one month or less who yet had lymph node metastases. There were other patients without any symptoms who, upon routine physical examination, were found to have rectal carcinomas that were later discovered to have metastasized. There were four patients with symptoms of 1 year's duration, one of 1.5 years, and another of 2 years, whose specimens showed no evidence of regional lymph node involvement. One of these patients was given up as hopeless 1.5 years prior to admission to this hospital. Duration of symptoms alone should not influence the treatment advised.

GROSS TYPES OF RECTAL CARCINOMAS

Carcinoma of the rectum was classified by its gross characteristics into three groups. The first group included the large, fungating, polypoid neoplasms, the majority of which arose in polypi. With these were included those carcinomas which were originally polypoid, but whose centers had undergone necrosis and ulceration so that they had become ulcerated with a polypoid, rolled, everted border. It was felt that central ulceration had occurred, either because of outgrowing their blood supply or because of ischemia as the result of neoplastic occlusion of the blood vessels. Most of them had marked infection and inflammatory changes within their substance. The second group included the sessile or plaquelike neoplasms which infiltrate the bowel wall. In the third group the lesion was excavated to form a deep ulcer. A correlation of these gross types with lymphogenous metastases (Table II) confirmed the opinion of others[6] that lesions tending to grow out into the lumen are less malignant than those infiltrating deeply into the wall.

TABLE II

CORRELATION OF GROSS TYPES AND LYMPH NODE METASTASES

GROSS TYPES	NUMBER OF CASES	WITH METASTASES	WITHOUT METASTASES	PERCENTAGE OF METASTASES
Excavating	3	1	2	33
Polypoid	28	15	13	53.5
Sessile	21	17	4	80.9

Of the 3 excavating lesions, only 1 (33 per cent) had metastasized; of the 28 polypoid neoplasms, 15 (53.5 per cent) had metastasized; whereas, in the 21 sessile neoplasms, 17 (80.9 per cent) had metastasized, showing that this latter type of malignancy has a very much higher probability of metastasizing. An excellent example of the lower grade of malignancy of polypoid carcinomas is illustrated by one of our patients who had a huge fungating polypoid neoplasm

measuring 11.5 by 7.5 cm. in diameter, beginning at the mucocutaneous junction, completely encircling the lumen, and extending upward as far as the finger could reach. This appeared to be fixed to the prostate anteriorly and was thought to be inoperable. This patient was a poor surgical risk because of his age, obesity, and hypertension. Because of intestinal obstruction, a sigmoid colostomy was done. No evidence of hepatic or peritoneal metastases was found. Two weeks later he died of pulmonary embolism. The entire lower abdominal and pelvic contents were dissected retroperitoneally and cleared, and 257 lymph nodes were isolated from the three zones of spread, including those along the abdominal aorta, the internal and external iliac vessels, and inguinal regions. No metastases were found. This case illustrates three points: (1) that huge lesions in themselves do not contraindicate resection, or at least laparotomy to determine operability; (2) that polypoid neoplasms tend less to metastasize; and (3) that fixation of the growth to the prostate may be inflammatory rather than neoplastic. Nevertheless, over 50 per cent of the polypoid neoplasms had metastasized and there is no means of determining which of these lesions have or have not done so. The one observation that is valuable is that sessile, plaquelike neoplasms have a high percentage of metastases.

METASTASIS AND LEVEL OF LESION

The lesions were classified according to their distance above the mucocutaneous junction in order to correlate location with the occurrence of lymphatic metastases. The neoplasms were divided into four groups: (1) those arising within the anal canal up to and including 2.5 cm. above the mucocutaneous junction; (2) those within the ampulla of the rectum, which we arbitrarily placed between 2.5 to 9.5 cm. above the mucocutaneous junction; (3) those of the rectosigmoid, which, according to anatomists, vary from 10 to 15 cm. above the mucocutaneous junction; and (4) those carcinomas arising from the sigmoid colon above 15 cm. from the junction.

There were 18 adenocarcinomas and 1 spindle-cell sarcoma arising within the anal canal and low rectum. Of these, 8 had not metastasized, and 11, including the spindle-cell sarcoma (57.9 per cent), had. Of those 11 neoplasms which had metastasized, 6 had spread along the superior zone in lymphatics accompanying the superior hemorrhoidal vessels as well as along the lateral zone of spread accompanying the middle hemorrhoidal vessels (Fig. 5*A*). In the remaining 5 cases, metastases were found along the superior zone of spread only (Fig. 5*B*). Of the 11 cases that had metastasized, 3 had three or less lymph nodes involved; in 2 of these the involved nodes were located at the primary site. In an additional 3 cases in which four or more nodes were involved, the positive nodes were located close enough to the primary site to be included in a perineal resection as far as the superior

zone of spread alone is concerned. Thus, 13 of the 19 cases (68.4 per cent) of the lesions in the anal canal and low rectum were amenable to perineal resection in respect to the superior zone of spread.

It is interesting to note, however, that seven specimens, or 36.8 per cent of the total of 19 cases in this region, showed evidence of lymph node involvement up to the margin of excision of the levator ani muscles along the lateral zone of spread (Fig. 5*A*). This emphasizes the importance of wide excision of the tissues of the lateral zone of spread as well as the superior zone of spread in operating on low-lying rectal carcinomas and those of the anal canal.

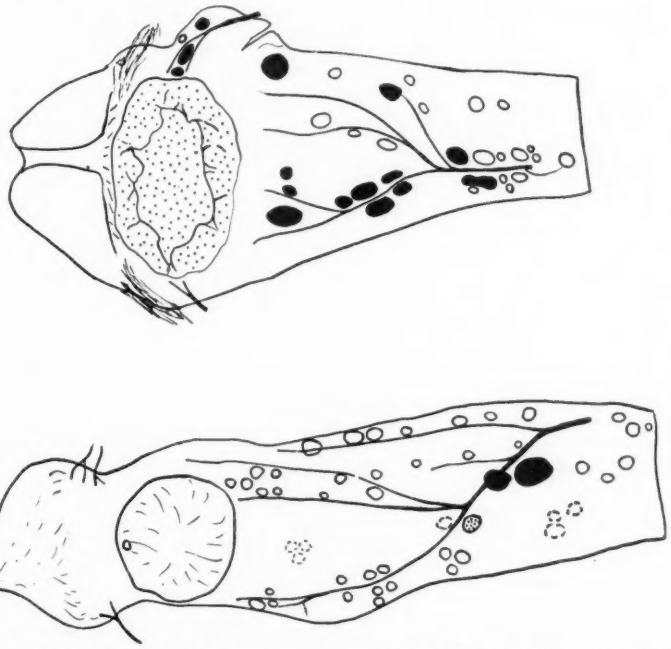

Fig. 5.—*A*, Line drawing illustrating a far-advanced adenocarcinoma mucosum, Grade III, of the anal canal; 33 lymph nodes isolated, 15 of which, lying along the superior and lateral zones of spread, are largely replaced by carcinoma. *B*, Line drawing illustrating an adenocarcinoma of the anal canal; 50 lymph nodes isolated, 3 of which, lying at a considerable distance from the primary site, are largely replaced by carcinoma.

Six cases (31.5 per cent) of the total 19 showed lymph node involvement along the superior zone of spread which would have been beyond the reach of a perineal resection (Fig. 5*B*). Of these 6 cases showing metastases in lymph nodes at a considerable distance above the primary neoplasm, 2 showed nodes to be involved up to the site of ligation of the superior hemorrhoidal vessels, so that in all probability there may be residual carcinoma, even following a combined abdominal-perineal resection. The specimen shown in Fig. 5*B* had no metastases to the immediate regional lymph nodes, but did have metastases in lymph nodes at a considerable distance above the lesion.

In summarizing this group, theoretically 68.4 per cent of the patients could have been completely cured by perineal resection if the lymphatic

spread of carcinoma were the only factor involved, but 31.5 per cent of the anal and low rectal lesions would not have been cured by perineal resection. However, 10.5 per cent (2 cases) probably were not cured because of high involvement of the lymphatics, by combined abdominal-perineal resection with high ligation of the superior hemorrhoidal vessels. Thus, 21.1 per cent more cases would be cured by the more extensive operation.

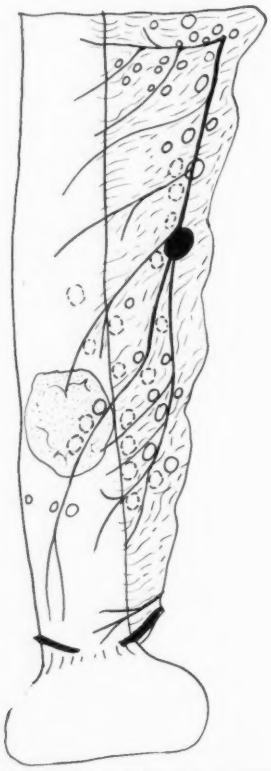

Fig. 6.—Line drawing illustrating an advanced papilliferous adenocarcinoma, Grade II, of the rectal ampulla; 50 lymph nodes isolated, 1 of which, lying 5 cm. from the primary site, is completely replaced by carcinoma.

There were 21 cases of carcinoma of the rectal ampulla, 8 without metastases and 13, or 61.9 per cent, with metastases. In every instance the lymphatic spread of carcinoma of the rectal ampulla was along the superior zone. Some of the lesions which were partly within the rectal ampulla but whose inferior edges were less than 2.5 cm. above the mucocutaneous junction have already been considered with the low-lying lesions. In no lesion of which the inferior border was 3 cm. or more above the mucocutaneous junction did we find metastases along the lateral zone of spread. Of the 13 cases with metastases in the lymph nodes, in 2 the involved nodes were confined to the region of the primary site; 2 more had positive nodes at least 5 cm. above the primary site (Fig. 6), and in 2 the metastases were 10 cm. or more away from the neoplasm without involvement of the intervening nodes.

In another case (Fig. 7*A*) nodes were invaded near the primary site and none involved until a point 10 cm. higher at the site of ligation of superior hemorrhoidal vessels. In other cases, such as Fig. 7*B*, nodes were involved in a continuous chain from the primary neoplasm to within a short distance of the site of ligation. Only one of the carcinomas in the rectal ampulla with metastases would have been suitable for a perineal resection. As seen in the diagrams of cleared specimens, the majority of cases present differences in direction of lymphatic spread between the lesions of the ampulla and of the rectosigmoid and sigmoid colon. The lymph node metastases of carcinoma of the ampulla lie along the lymph channels which accompany the vessels so that they

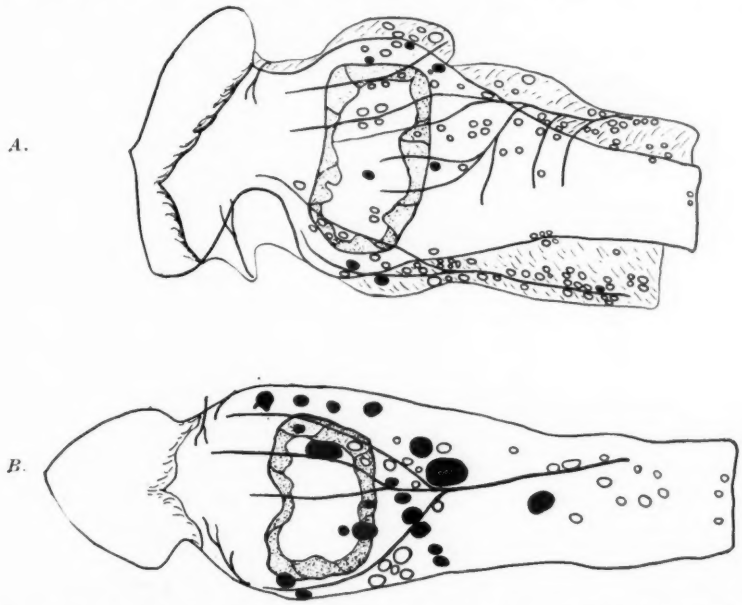

Fig. 7.—*A*, Line drawing illustrating an adenocarcinoma, Grade II, of the rectal ampulla; 123 lymph nodes isolated, 7 of which, near the primary site, and 1 at the level of ligation of the superior hemorrhoidal artery, show metastatic carcinoma. *B*, Line drawing illustrating an adenocarcinoma mucosum, Grade II, of the rectal ampulla; 46 lymph nodes isolated, 19 of which, about the primary site and in a continuous chain nearly to the level of ligation of the superior hemorrhoidal artery, are largely replaced by metastatic carcinoma.

run upward almost parallel with the course of the rectum. Consequently, the lesions of the ampulla must be more widely excised than those of the rectosigmoid colon where the lymph channels tend to run perpendicular to the bowel. Lesions of the rectosigmoid and sigmoid should have a greater depth of mesentery excised. It will be noted also that there were fewer involved lymph nodes for each case in carcinoma of the ampulla than in lesions of the anal canal and low rectum.

There were six cases of carcinoma of the rectosigmoid. Five of these (83.3 per cent) had metastasized, only one node being involved in two instances; two in the third (Fig. 8*A*), the involved nodes being adjacent to the primary site; and in the other two cases, lymph nodes were in-

volved 5 and 10 cm. above the primary site. There was evidence of retrograde metastases in one of these cases in that one positive node was located 1.5 cm. below the lesion. Considering only regional lymph node involvement, four cases (66.6 per cent) would have been just as suitable for wide resection with preservation of the low rectum as for combined abdominal-perineal resection.

There were 6 cases of carcinoma above the rectosigmoid junction in the group. All of the involved nodes in the 4 cases which had metastasized to lymph nodes were located near the primary site (Fig. 8*B*), making them also suitable for reconstructive operation as far as lymphogenous metastasis is concerned.

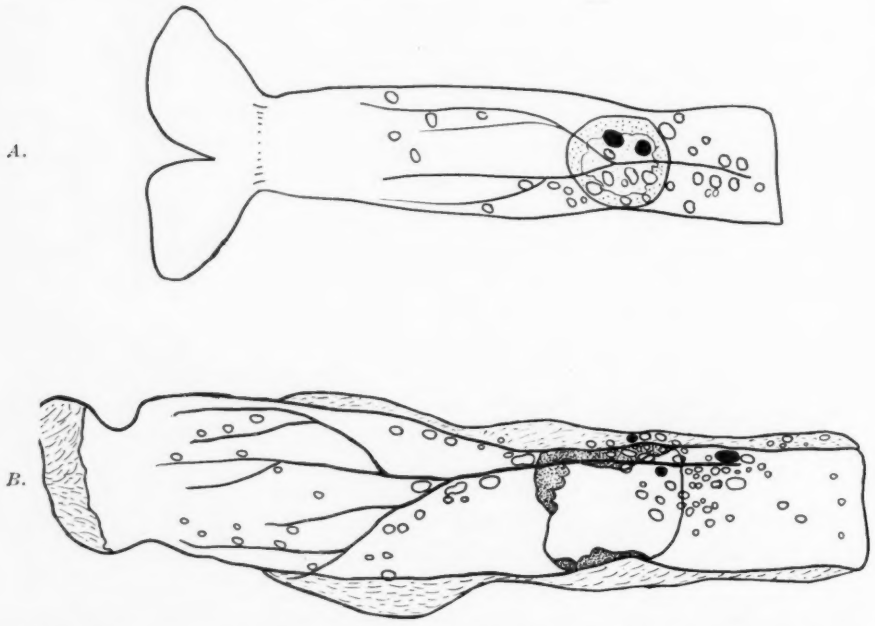

Fig. 8.—*A*, Line drawing illustrating an advanced ulcerative papilliferous adenocarcinoma, Grade III, of the rectosigmoid, infiltrating through the wall and into adjacent adipose tissue; 35 lymph nodes isolated, 2 of which show metastatic carcinoma at the primary site. *B*, Line drawing illustrating a widespread infiltration of adenocarcinoma, Grade II, of the low sigmoid colon; 88 lymph nodes isolated, 3 of which, lying near the primary site, show metastatic carcinoma.

SITE OF ORIGIN UPON CIRCUMFERENCE OF BOWEL WALL AND METASTASES

There have been varying opinions expressed as to the site of origin upon the circumference of the bowel wall and the likelihood of metastases. Any correlation of this sort is difficult because rarely, unless the lesion is very small, is it confined to one wall alone. Usually the lesion involves several walls and often is annular. If the lesion was of such a size as to involve two walls, i.e., anterior and lateral walls, we classified it as such; in an extensive lesion it was placed with that part corresponding to its center. In the correlation, the anterolateral and posterolateral lesions were classified in either the anterior or posterior

group and to the lateral wall group. Eight cases of annular neoplasm in which the site of origin was impossible to determine were excluded. The anterolateral and posterolateral lesions were considered as being either upon the posterior or anterior wall. It appeared that the anterior wall neoplasms were slightly more likely to metastasize. This observation is even more striking when these same neoplasms, i.e., those on the antero- and posterolateral walls, were in the lateral group. In this particular instance 85.4 per cent of those on the anterior or antimesenteric wall had metastasized to the regional lymph nodes.

SIZE OF NEOPLASMS AND METASTASES

There was found no relation between the size of the lesion and the presence of metastases. The average size of all lesions was 5.8 by 4.5 cm. There were 8 cases without metastases and 18 cases with metastases in lesions of less than average size. In the group of neoplasms larger than average size, there were also 8 cases without metastases and 18 cases with metastases. The 10 smallest carcinomas and the 10 largest carcinomas were compared, and in each group there were 6 cases with and 4 cases without metastases. The two largest carcinomas, whose areas were 85 and 79.25 sq. cm., respectively, had no metastases. The next largest size was 49 sq. cm. and this also had not metastasized to the lymph nodes. The largest size to have metastasized was 42.5 sq. cm. and this case had only two positive lymph nodes in 51.

EXTENT OF BOWEL CIRCUMFERENCE INVOLVED AND METASTASES

Whereas there was no relationship between the size of the carcinoma and the lymph node metastases, it seems true that there is a slight increase in likelihood of metastases as more of the bowel circumference is involved by the malignancy. The neoplasms were divided into four groups, depending upon the percentage of the bowel circumference involved (Table III). There was a slightly increasing tendency for the neoplasm to metastasize as it spread around the bowel wall. It appears that the extent of the circumference involved is of more importance in determining the likelihood of metastases than the longitudinal extent of the lesion.

TABLE III

CORRELATION OF CIRCUMFERENCE OF WALL INVOLVED AND METASTASES

PERCENTAGE OF CIRCUMFERENCE INVOLVED	NUMBER OF CASES	WITHOUT METASTASES	WITH METASTASES	PERCENTAGE WITH METASTASES
0–25	4	2	2	50
25–50	10	4	6	60
50–75	22	8	14	63.6
75–100	17	5	12	70.6

DEGREE OF CELLULAR DIFFERENTIATION (GRADING) AND METASTASES

Most of the carcinomas of the rectum were graded II and III as to cellular differentiation. There was only one Grade IV neoplasm, a carcinoma developing in a bowel the site of a chronic ulcerative colitis in a girl 24 years old. The entire rectum and rectosigmoid, except for the anal canal, were found to be infiltrated diffusely by a poorly differentiated adenocarcinoma that had spread through the entire wall and showed carcinomatous cell nests in both the lymph and blood channels. Seventy of 100 lymph nodes isolated were largely replaced by metastatic carcinoma. The patient died three months later, at which time she showed further carcinomatous proliferation in the transverse and ascending colon. The only carcinoma graded I, not listed in the table, was found in a polyp which accompanied a large carcinoma. Table IV substantiates the dictum that the more anaplastic the lesion, the more likely the presence of lymph node metastases. However, the surgeon should not base his surgical procedure solely upon histologic grading of biopsy specimens. It is a common experience to find that, after having examined the specimen as a whole, the opinion based on the biopsy must be altered. It is impossible to grade the carcinoma as a whole by examining only one small portion of it. Degree of malignancy, size of lesion, and operability are not synonymous terms and should not be used interchangeably. Often the more malignant neoplasms are the smaller and in turn are the more favorable operative cases from the technical aspect. These lesions are highly malignant and give rise to early metastases. An illustration that grading of the biopsy specimen does not represent the tumor as a whole is shown in a case in which the biopsy specimen was taken at the infiltrating border and graded IV. Because the lesion was assumed to be very highly malignant, fixed to the prostate, and because the patient was a poor operative risk, a palliative colostomy only was done. The patient died and the autopsy specimen showed a moderately well-differentiated adenocarcinoma, graded III, with no evidence of metastases.

TABLE IV

CORRELATION OF GRADE OF MALIGNANCY AND METASTASIS

GRADE	NUMBER OF CASES	WITHOUT METASTASES	WITH METASTASES	PERCENTAGE WITH METASTASES
I	0	0	0	0
II	33	14	19	57.5
III	18	5	13	72.2
IV	1	0	1	100

Gabriel, Dukes and Bussey[7] classified carcinomas of the rectum into Groups A, B, and C. Group A included cases where the carcinoma infiltrated well into the wall but not into the perirectal tissues; Group B, those in which the carcinoma extended into the perirectal tissue;

and Group C, those having positive lymph node metastases. They found that 91 per cent of Group A cases and 64 per cent of Group B cases were alive for five years or more following operative removal; whereas, in Group C, those having glandular metastases, only 18 per cent survived five years. This classification in its last analysis really compares the prognosis of cases with metastases and those without. It was difficult for us to fit our cases into this classification. We had 30 cases in which the malignancy was confined to the rectal wall. Of these, 13 (43.3 per cent) had metastasized to the regional lymph nodes; whereas we had 22 cases which had infiltrated into the perirectal tissues, of which 20 (90.9 per cent) had given rise to metastases. This comparison, we believe, is of more value.

The histologic types of carcinoma and the percentages of metastases are shown in Table V. The most common type was adenocarcinoma; the next most common was papilliferous adenocarcinoma, several of which were papilliferous cystadenocarcinoma. The likelihood of metastases of these types is approximately the same, in that 61.2 per cent of the first and 61.5 per cent of the second gave rise to lymph node involvement. There were four cases of adenocarcinoma mucosum, all of which had metastasized and in which the extent of metastases was also great. Adenocarcinoma mucosum is generally considered to be the most malignant type, this observation being borne out by this small series. There were three cornifying squamous-cell carcinomas of the anal canal and mucocutaneous junction; another, which was partly adenocarcinoma and partly cornifying squamous-cell carcinoma; and one spindle-cell sarcoma.

TABLE V

CORRELATION OF MICROSCOPICAL TYPES AND METASTASES

MICROSCOPICAL TYPES	NUMBER OF CASES	WITHOUT METASTASES	WITH METASTASES	PERCENTAGE WITH METASTASES
Adenocarcinoma	31	12	19	61.2
Papilliferous adenocarcinoma	13	5	8	61.5
Adenocarcinoma mucosum	4		4	100
Cornifying squamous-cell carcinoma	3	1	2	66.6
Adenocarcinoma and squamous cell	1	1	0	0
Spindle-cell sarcoma	1		1	100

Finally, the point that has been brought out by numerous other observers, but which can be re-emphasized, is the close relationship between carcinoma of the rectum and rectal polyps. In the 53 cases studied, there was microscopic evidence of the malignancy arising upon pre-existing polyps in 28.3 per cent of the cases (15 of 53 cases). Twenty-two other cases (41.5 per cent) also had associated polyps,

varying from one to six polyps per specimen. Examination of one such polyp 3 mm. in diameter showed early carcinomatous proliferation. Two additional cases were associated with polyposis of the colon. There is microscopic evidence to show the progression from simple hyperplasia of the rectal mucosa through the formation of small adenomas or polyps, to the development of frank carcinoma. Both the sessile and larger pedunculated polyps may show marked atypical hyperplastic proliferation of the mucous membrane but no infiltrative growth. It is not necessary for the polyp to be either large or pedunculated, for very small, innocuous-appearing, sessile polyps may be the basis of malignant change.

SUMMARY

A study was made of metastasis from carcinoma of the rectum and rectosigmoid to the regional lymph nodes in 53 specimens, and an average of 68 nodes per operative specimen were isolated and examined microscopically. They were charted and the results correlated with various physical attributes of the associated primary lesion.

Lymph nodes were found at the site of metastases in 64 per cent of the carcinomas of the rectum and 15 per cent showed invasion of the blood vessels.

Age of the patient had no important influence on the presence of metastases in lymph nodes as 70 per cent of the patients below 50 years of age had them, while of those over 50 years, metastases were present in 60 per cent.

A comparison of the incidence of metastases in carcinoma of the rectum classified according to their gross characteristics as sessile, excavating, and polypoid showed 80.9 per cent of the sessile type to have produced metastases; in 33 per cent of the excavating and only 53.5 per cent of the polypoid neoplasms had this occurred.

The only lesions having involvement of lymph nodes along the lateral zone of spread were those arising between the mucocutaneous junction and a point 3 cm. above it.

In no instance was found retrograde metastasis to a significant level below the primary lesion. No relation was found to exist between the size of the tumor and the presence of metastases in lymph nodes.

No correlation was found between the size of the lymph nodes and the presence in them of metastases.

If the lesion had infiltrated through the wall of the rectum, lymph nodes were involved in 90.9 per cent in comparison to those lesions that were still confined to the wall in which 43.3 per cent had metastases in lymph nodes.

As far as could be determined, 28 per cent of the neoplastic lesions developed in polyps and another 41.5 per cent of the specimens had benign polyps present.

Neoplasms arising on the anterior wall had the larger percentage of lymph node metastases.

Involvement of lymph nodes and operability are not dependent on duration of symptoms.

Surgical procedure should not be based solely on the histologic grading of biopsy specimens.

The prognosis in any case can be made more accurately by an examination of all of the lymph nodes.

In spread of carcinoma along any zone of diffusion the nodes are not necessarily involved in continuity but may be involved at some distance with normal nodes intervening between the primary site and the metastases.

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INTERNAL SUPRAVESICAL HERNIAS

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THIS REVIEW and discussion of internal supravesical hernias, including a report of an additional case, show that this condition is much less rare than previously believed, that a preoperative diagnosis of the condition is difficult but possible, and that the prognosis in each case depends upon early proper treatment.

Authors have disagreed on the anatomic terminology in describing the site of the lesion as well as on the nomenclature of the hernias originating in the supravesical fossa. Our conclusions have been reached after a review of all available literature on this subject.

ANATOMY

The supravesical fossa is a triangular area bounded laterally and above by the lateral umbilical folds which cover the obliterated umbilical arteries, and below by the peritoneal reflection that passes from the anterior abdominal wall to the fundus of the bladder. The median umbilical fold, formed by the remnant of the urachus, divides the supravesical fossa into right and left halves. Pick[1] and others believe this area should extend posteriorly along each side of the bladder to the point where the lateral umbilical folds blend into the peritoneum of the true pelvis and thus include the retrovesical fossa in the male and the vesicouterine fossa in the female. Very few authors agree with this extension of the limits of the fossa because it would make the boundaries too obscure and too inclusive.

Supravesical fossa is the name most widely accepted since its introduction by Waldeyer[2] in 1874. Other names used to designate this region are: vesicoinguinal fossa by Velpeau,[3] fossa vesicomedialis by Brentano,[4] fossa interligamentosa by Draudt,[5] internal inguinal fossa by Kadlicky,[6] fovea medialis by Cestmir,[7] paravesical fossa by Pick, and the fovea inguinalis intima by Joessel.[8]

NOMENCLATURE OF HERNIAS

The chaotic multiplicity of terms used in the past in referring to internal supravesical hernias can be illustrated by enumerating twenty-two of them in the order in which they have appeared in publications. Ring[9] first described a case as an internal inguinal hernia in which he referred to Cooper's[10] work published in 1804 (Fig. 1). Other names used were: hernia inguinalis media antevesicalis by Parise,[11] properitoneal diverticula with intestinal incarceration by Hartung,[12] hernia retroperitonealis parietalis hypogastrica by Linhart,[13] anterior retro-

peritoneal hernia by Klebs,[14] properitoneal hernia by Kronlein,[15] vesicopubic hernia by Havage,[16] hernia diverticula parietoinguinalis, a later name used by Kronlein to differentiate it from herniae *en bissac*, oblique internal or suprapubic inguinal hernia by Lupo,[17] prevesical hernia by Kaufmann,[18] anterior retroperitoneal hernia by Wilms,[19] supravesical hernia by Waldeyer, prevesical epiplocele in a case of Makins[20] which contained omentum, properitoneal supravesical hernia by Maydl,[21] hernia inguinalis obliqua interna by Joessel, prevesical properitoneal hernia by Kadlicky, retroperitoneal bladder hernia of the supravesical fossa by Steimker,[22] oblique internal hernia by Luttel-

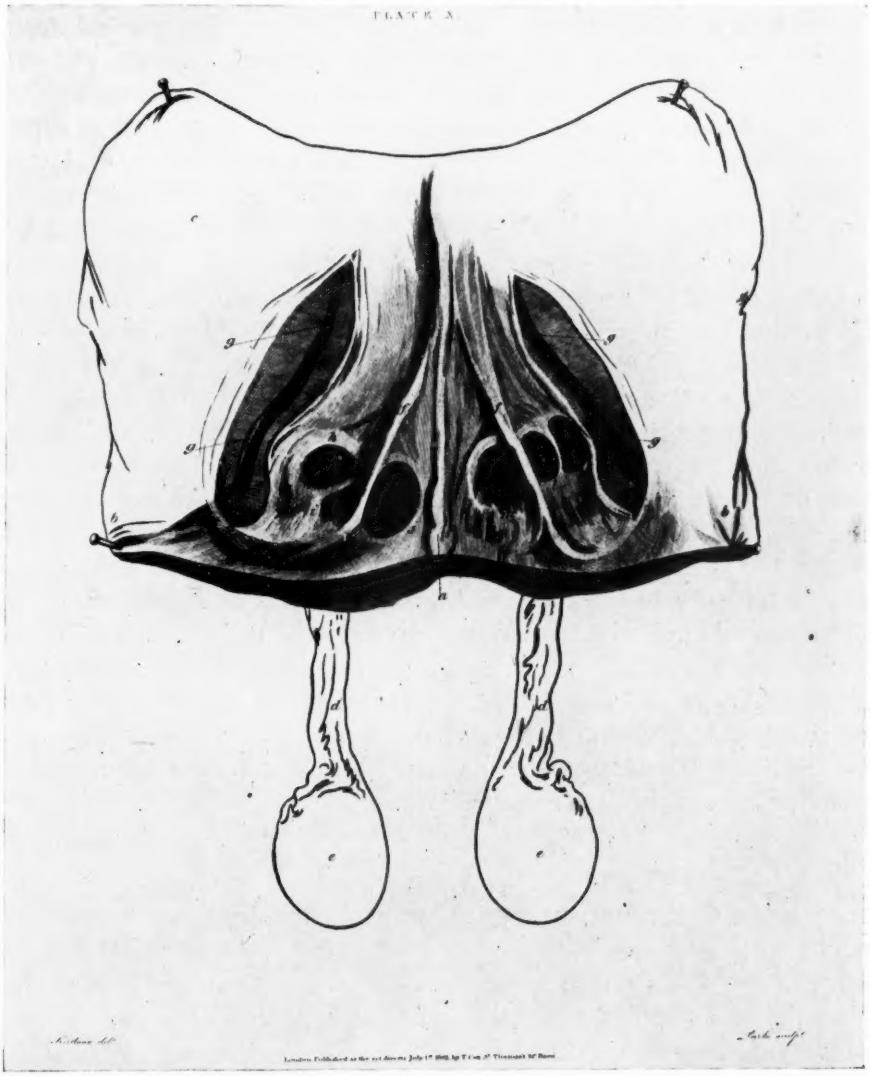

Fig. 1.—This plate appeared in Sir Astley Cooper's book *The Anatomy and Surgical Treatment of Internal and Congenital Hernia*, published in 1804. It shows six hernial openings, two of which are in the supravesical fossa. This is probably the first reference to supravesical hernia.

mann,[23] and paravesical hernia by Pick. In addition there were four terms noted by Blum[24] which had been used by various authors when an internal supravesical hernia protruded into the bladder apex which were: intravesical hernia of the supravesical fossa, invaginatio vesicae, inversio vesicae urinariae incompleta, and cystanestrophe. This varied nomenclature may explain why there have been but six authentic cases of supravesical hernias collected in the past.

The logical name is one indicating the place of origin of the hernia with added terms to indicate the direction taken by the herniation, the place of lodgement of the hernial sac, and possibly the character of the hernial contents. With this in mind we believe the term supravesical is the most suitable for hernias originating in the supravesical fossa. These hernias can be further classified into external, internal, and perhaps interstitial types. The external types appear in the hypogastrium or in the inguinal, femoral, and obturator regions. The internal supravesical hernias can be prevesical, intravesical, paravesical, or lateral dependent upon lodgement in the space at Retzius, in the bladder, beside the bladder, or in the more lateral pelvis respectively. Definite examples of interstitial types have not been recorded.

Other classifications and terms are not acceptable because they are misleading and indefinite. The classification of Walker[25] included only three possible types which he recognized as arising from the supravesical fossa. They were prevesical for the internal type, hypogastric for those appearing directly anteriorly and externally, and a third group described as passing through the femoral canal and often mistaken for true femoral hernias. The term prevesical, when used alone to designate internal supravesical hernias in the space of Retzius, is misleading because hernias originating in the inguinal regions may extend medially to the prevesical space as exemplified by the case reports of Makin, Parise, and Oberst.[26] Also the use of the term paravesical alone, as applied to supravesical hernias by Pick, has the same objection, since hernias arising in the inguinal region may extend medially as they descend into the pelvis and may lodge in the paravesical space adjacent to the bladder. Kaufmann reported a case of this kind.

ETIOLOGY AND PATHOGENESIS

According to Finsterer,[27] the primary etiologic factor underlying the formation of supravesical hernias is an abnormality in the regression of fetal structures causing a congenital predisposition to hernias because of the depth of the supravesical fossa. Rokitansky[28] also emphasizes the part played by raised fibrous bands, due to delayed regression of the umbilical arteries and urachus, so that they stand out from the anterior abdominal wall raising mesentery-like peritoneal folds and forming deep fossae between them. These fossae further develop into deep diverticula due to the loss of prevesical fat, fibrotic retraction

following subperitoneal inflammations, peristaltic action of lodged loops of intestines, the dilating wedge effect of omentum or lipomas of the bladder, and finally because of sex differences in pelvic anatomy and physiology so that males are more often affected. The bladder filling in males causes an anterosuperior enlargement that traps intestines in supravesical diverticula when present, while in the female the distention of the bladder occurs laterally and forces supravesical diverticular contents upward and outward.

General etiologic factors in common with the formation of hernias elsewhere are: congenital weakness of connective tissue with concomitant hernias at other sites, fatty infiltration of connective tissue during obesity so that weight loss results in pathologic enlargement of natural openings, and persistent organic or repeated functional increases in intra-abdominal pressure which cause peritoneal outpouchings at the weakest points.

After a supravesical diverticulum has developed it can herniate in any one of five possible directions, depending upon the path of least resistance (Fig. 2). Those of the superomedial part, making up the greatest number of cases, protrude externally in the hypogastrium. Those of the superolateral part evaginate toward the inguinal, femoral, or obturator regions. The inferomedial protrusions become lodged in the prevesical space of Retzius or when the bladder apex is weakened by defective closure of the urachus, as in cases reported by Forster[29] and Markel,[30] they herniate directly into the bladder. The fifth possibility is the extension of the herniation caudally as far as the prostatic bed lateral to the bladder in the male, or to the base of the broad ligament in the female. The last three groups arising from the inferior portion of the fossa never appear externally because they are below the rigid wall of the anterior pelvis.

Spontaneous reduction of internal supravesical hernias can occur, as evidenced by finding empty hernial sacs after symptoms of visceral lodgement. Korte[31] reports 1 case and Robinson[32] 2 cases in living subjects; while Reich,[33] Pick, Tandler and Halban,[34] and Marconi[35] report a total of 8 cases of empty hernial pockets found post mortem. Cooper's case was probably also of this type.

Hernias originating in the supravesical fossa are more numerous than the reviews of the past indicate. A multiplicity of names applied to these hernias reported in various languages has apparently been a source of difficulty in attempted reviews. That these hernias have been overlooked is attested by the absence of a definition of the term in modern medical dictionaries as well as by the absence of any reference to them in such publications as Watson,[36] Carrera,[37] and numerous earlier works.

Supravesical hernias appearing externally are most numerous. Reich[38] reviewed 26 cases in 1909 and several publications have appeared on

TABLE I

NO.	AUTHOR	DATE	AGE	SEX	LOCATION	CONTENTS OF SAC	DURATION OF SYMPTOMS	TYPE	RESULTS
1	Cooper	1804		M	Supravesical fossa, bilateral	Peritoneal sac covering bladder diverticulum	Long	Reducible	Died, cause unknown
2	Ring	1804	23	F	Right supravesical into prevesical space	Strangulated omentum size of a hen's egg	6 days	Strangulated omentum	Died sixth day; no operation
3	Linhart	1856			Supravesical into prevesical space	Small intestine	Asymptomatic	Accidental postmortem finding	Died from other causes
4	Havage	1878	58	M	Right supravesical into prevesical space	Loop of intestine size of walnut	13 days	Strangulated gangrenous, perforated	Died thirteenth day; no operation
5	Lupo	1881	50	M	Right supravesical fossa through transversalis fascia lateral to rectus muscle	Loop of small intestine with hypertrophied walls	Asymptomatic	Incarcerated; incidental postmortem finding	Died, cause unstated
6	Aschoff	1896	61	M	Left supravesical fossa into medial inguinal fossa	Small intestine	3 days	Strangulated but viable	Recovered after operation
7	Brentano	1897	45	M	Left supravesical fossa to prevesical space	8 cm. of small intestine	3 days	Strangulated but viable	Recovered after operation
8	Maydl	1898	Old	M	Right supravesical fossa, bilateral	Small intestine in one, fatty tumor in other	Acute	Strangulated intestine	Died without operation
9	Waldeyer	1899	Old	M	Left supravesical fossa to medial inguinal fossa	Mass of omentum size of hazelnut	Asymptomatic	Incidental postmortem finding	Died, cause unknown
10	Calabi and Gaiardoni	1902	60	M	From supravesical fossa into bladder	Intestinal loop	1 yr. after blow on abdomen	Strangulated by bladder wall musculature	Died without operation
11	Blum	1904	23	M	Left supravesical fossa to prevesical space	Small intestine	1 yr.	Strangulated	Died without operation

12	Dall 'Acque	1907	36	M	Left supravesical fossa to prevesical space	Peritoneal sac empty at autopsy	Unknown duration	Reduced spontaneously	Died of other causes
13	Jaehne	1908	22	M	Right supravesical fossa to prevesical space	20-25 cm. of intestine	14 days	Strangulated and gangrenous	Lived but fecal fistula remained
14	Fromme	1908	59	M	Left supravesical fossa toward obturator foramen	10 cm. of small intestine	14 days	Strangulated	Recovered after operation
15	Reich	1909	62	M	Left supravesical fossa into prevesical space	10 cm. of small intestine and some incarcerated omentum	5 days	Strangulated intestine, incarcerated omentum	Died after operation
16	Reich	1909	75	M	Right supravesical fossa toward obturator foramen	11 cm. of small intestine	24 days	Strangulated	Died after operation
17	Trnka	1913	57	M	Left supravesical fossa to prevesical space	10 cm. of small intestine	3 days	Strangulated and gangrenous	Recovered from operation
18	Shuttze	1916	34	M	Right supravesical fossa laterally into inguinal region	Small intestine	9 wk. of intermittent ileus	Incarcerated intestine	Results not given
19	Luttelmann	1919	67	F	Right supravesical fossa to prevesical space	12 cm. of intestine	9 mo. chronic, 9 days acutely ill	Strangulated and gangrenous intestine	Recovered after operation
20	Luttelmann	1919	26	M	Supravesical fossa toward femoral region	Omentum and diverticulum of bladder	Few months	Incarcerated	Recovered after operation
21	Bayer	1922	58	M	Right supravesical fossa to prevesical space	Small intestine	3 days	Strangulated and gangrenous intestine	Died after operation
22	Vogeler	1925	55	M	Left supravesical to prevesical space	Small intestine	2 mo.	Reducible	Recovered after operation
23	Belu	1925	32	M	Left supravesical to prevesical space	Small intestine	Acute	Strangulated and gangrenous intestine	Died after operation
24	Schiele	1926	44	M	Left supravesical to prevesical space	Loop of lower ileum	6 days	Incarcerated	Recovered after operation

TABLE I—CONT'D

NO.	AUTHOR	DATE	AGE	SEX	LOCATION	CONTENTS OF SAC	DURATION OF SYMPTOMS	TYPE	RESULTS
25	Kudrnac	1926	25	M	Center of supravesical fossa to prevesical space	20 cm. of gangrenous small intestine	Chronic	Strangulated, gangrenous intestine	Not reported
26	Kudrnac	1926	46	F	Supravesical to paravesical space	8 cm. of small intestine	Acute	Strangulated, gangrenous intestine	Not reported
27	Cestmir	1928	26	M	Supravesical to prevesical space	5 cm. of small intestine	18 hr.	Strangulated	Recovered after operation
28	Cestmir	1928	53	M	Left supravesical to prevesical space	10 cm. of small intestine	2 days	Strangulated	Recovered after operation
29	Watschugoff	1931	24	M	Left supravesical to prevesical space	Small intestine	24 hr.	Strangulated	Recovered after operation
30	Watschugoff	1931	50	M	Left supravesical to prevesical space	12-15 cm. of intestine	4 days	Strangulated	Recovered after operation
31	Watschugoff	1931	29	M	Supravesical to prevesical space	Small intestine	24 hr.	Strangulated	Recovered after operation
32	Walker	1933	51	M	Right supravesical to prevesical space	Small intestine (ileum)	4 days	Strangulated	Recovered after operation
33	Walker	1933	63	M	Right supravesical to prevesical space	Loop of ileum	2 days	Strangulated	Recovered after operation
34	Kochaj and Wolf	1934	65	F	Left supravesical to prevesical space	75 cm. of small intestine	Intermittently for several years; obstruction, 2 days	Strangulated	Recovered after operation
35	Kochaj and Wolf	1934	62	M	Right supravesical to prevesical space	15 cm. of small intestine	3 days	Strangulated	Died after operation
36	Finsterer	1937	75	M	Right supravesical to prevesical space	10 cm. of ileum	30 hr.	Strangulated intestine, gangrenous	Recovered after operation
37	Stalker and Gray	1939	61	M	Right supravesical to prevesical space	Loop of ileum	3 days	Strangulated but viable	Recovered after operation
38	Warvi and Orr	1940	67	M	Right supravesical to prevesical space	10 cm. of ileum	2 wk. intermittent, 10 days last continuous attack	Strangulated but viable	Died after operation

the subject since that time. We will not discuss the external types for they do not present important diagnostic or therapeutic problems.

Internal supravesical hernias are rare and difficult to diagnose. Thirty-seven cases have been recorded in the literature completely enough to tabulate essential facts and group them as authentic cases (Table I). Three authors, Szabo,[39] Ornatauyan,[40] and Kramareuko,[41] have been referred to by others as having reported true cases of internal supravesical hernias, but we have been unable to secure their publications for confirmation. Cases have been omitted from the tab-

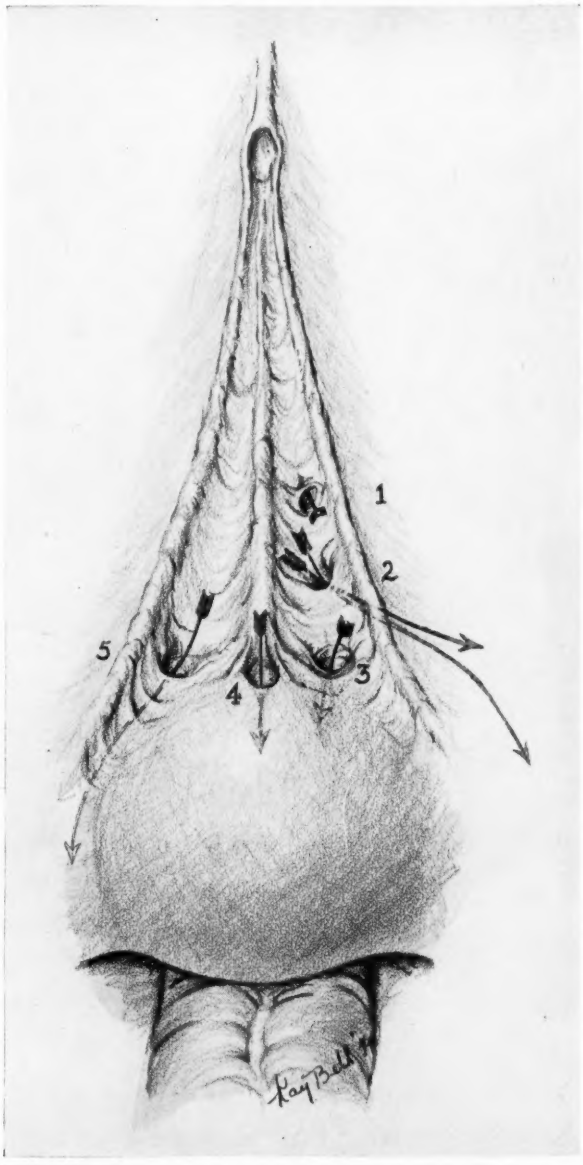

Fig. 2.—Sketch of supravesical fossa showing the five directions in which hernias arising in this fossa generally extend: *1*, to hypogastrium (external); *2*, to inguinal, femoral or obturator rings (external); *3*, to prevesical space; *4*, to fundus of bladder; *5*, to paravesical space.

ulation of true cases of supravesical hernias because of inadequacy of reports which have left the sites of origin and of the hernias in doubt. These are recorded by Cloquet,[42] Goyrand,[43] Velpeau, Monari,[44] Santuci,[45] Hutchinson,[46] De Grinocoli,[47] Kostanecki,[48] Kaufmann, Draudt,[5] Textor,[49] Kirchner,[50] Deus,[51] Foubert,[52] Trnka,[53] Hartung, and Luttelmann. Watschugoff[54] stated that 16 cases had been reported prior to his article, but he did not give any definite references or details. If these possible cases could be proved and added there would be a total of over 60 cases of internal supravesical hernias recorded in the past. In addition there are 11 cases which have been described with empty internal supravesical hernial pockets to which we have already referred. Watschugoff found 3 internal supravesical hernias in 1,500 hernia operations and estimated that 0.2 per cent of all hernias are of this type.

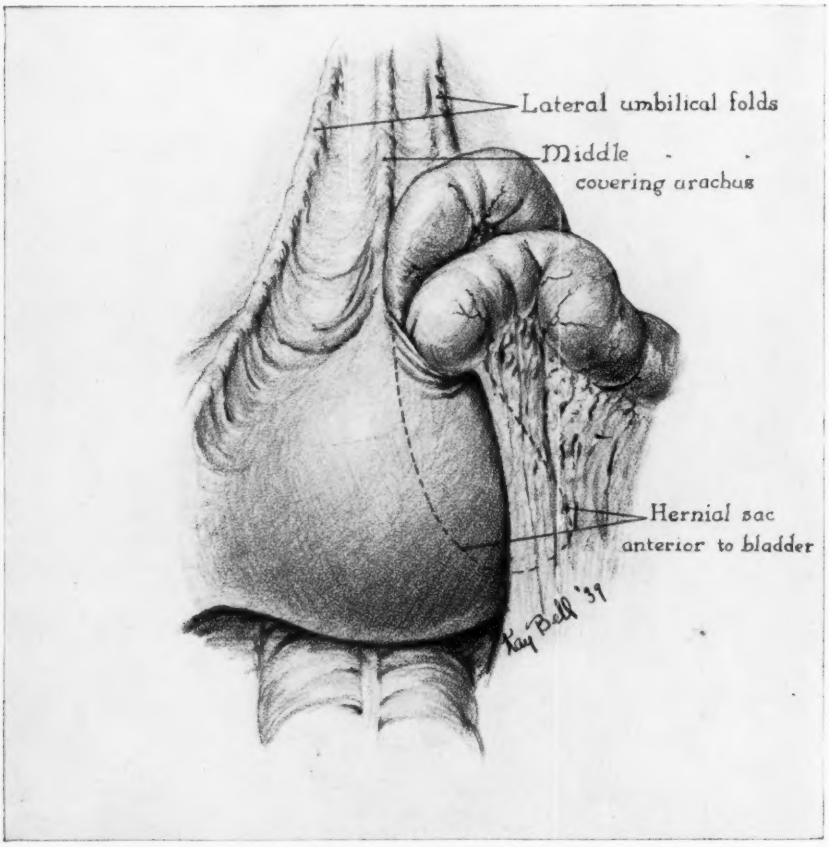

Fig. 3.—This sketch shows location of hernia reported here.

CASE REPORT

We here record an additional case of typical supravesical hernia with an illustration showing its extension into the prevesical space (Fig. 3).

T. S., a male, aged 67 years, was admitted to the University of Kansas Hospitals June 29, 1938. The chief complaints were abdominal pain and vomiting.

The illness began two weeks before admission with generalized cramping pains in the abdomen followed by vomiting. These symptoms persisted for three days and gradually subsided. He was free from symptoms for a week when the acute symptoms recurred. When admitted to the hospital he had been ill four days. During this time he had generalized abdominal pain, more pronounced in the lower abdomen, and persistent vomiting. He was very much prostrated and complained of some palpitation and occasional dyspnea. There was a history of nocturia with some difficulty in starting the urinary stream.

He appeared acutely ill and was obviously very weak. There was some abdominal distention and abdominal tenderness. The tenderness was chiefly confined to the lower abdomen. The inguinal rings were enlarged, but a hernia could not be found. The prostate was enlarged and somewhat tender. He had 125 c.c. of residual urine. A scout film of the abdomen, taken the morning after admission, showed a small amount of gas in three short coils of the small intestine. The second day a barium enema revealed nothing of pathologic importance except diverticula.

The morning following admission the blood chemistry showed a nonprotein nitrogen of 115 mg.; creatinine, 4.4 mg.; and chlorides, 270 mg. per 100 c.c. of whole blood. The red and white blood counts were within normal limits. There was a trace of albumin and a few pus cells in the urine. Intestinal obstruction was suspected, but, because of the blood chemistry findings, uremia was considered a possible cause of the abdominal distention. After six days' observation and treatment with intravenous dextrose and Ringer's solution, an exploratory abdominal operation was done through a right rectus incision. An opening 2 cm. in diameter was found near the apex of the bladder to the right of the peritoneal fold of the urachus in which was incarcerated a loop of ileum 10 cm. long. The fibrous ring of the opening was enlarged and the bowel easily freed. The bowel was constricted at the ring but still viable. The hernial sac was about 6 cm. long and extended downward in front of the bladder and to the right behind the right conjoined tendon. The sac was freed, removed, and the defect in the peritoneum closed.

The general condition of the patient did not improve following the operation. The abdominal wound disrupted on the fifth postoperative day and death occurred two days later. An autopsy was not permitted. The clinical and x-ray findings were typical of bronchopneumonia.

DIAGNOSIS

Walker, Stalker and Gray[55] and others state that a definite preoperative diagnosis of internal supravesical hernia has never been made nor do they believe that it will be made in the future. Fromme[56] did make this diagnosis on the basis of typical clinical findings confirmed by a cystoscopic visualization of a bulging of the anterior bladder wall caused by a prevesical hernia. Weil[57] states that Draudt is also said to have made the diagnosis preoperatively, but the report of Draudt's case is not complete enough to classify it as a supravesical hernia. Reich and Wildegans[58] believe it possible to make a correct clinical diagnosis of internal supravesical hernias.

The type of patient usually afflicted with an internal supravesical hernia is a well-nourished male between the ages of 22 and 74 years with a history of having lost some weight before the onset of symptoms.

Symptoms occur only with visceral retention in the internal supravesical hernial sac. They are usually those of acute intestinal obstruc-

tion with small bowel strangulation. Because of the enroachment upon the bladder, urinary symptoms are common. Symptoms that Reich considers pathognomonic are intestinal distention and tenderness directly over the bladder with other manifestations of intestinal obstruction. Because of the advanced age of many patients, bladder symptoms may be interpreted erroneously as being due to disease of the prostate.

In making a diagnosis the signs and symptoms of acute intestinal obstruction are readily interpreted. A scout film is a diagnostic aid. A cystoscopic examination of the bladder may be made for evidence of pressure deformity if the condition of the patient will permit. Tenderness in the bladder region with symptoms of acute bowel obstruction suggests the possibility of strangulation in the bladder area. Very frequently the serious condition of the patient will make prolonged and repeated examinations dangerous.

TREATMENT AND PROGNOSIS

The treatment is that of acute intestinal obstruction with strangulation. The necessity of intestinal resection increases morbidity and mortality. It is usually not advisable to free the sac in this type of hernia for the patient may not tolerate extensive surgery and removal of the sac does not improve the results. Most authors advise simple freshening of the edges of the hernial sac and closing it with a continuous suture with an added covering of the peritoneal fold most accessible. Reexpansion of the urinary bladder soon obliterates the space previously occupied by the hernia.

Of the 34 cases in Table I with known results there were 15 deaths, or a mortality rate of 44.1 per cent.

SUMMARY AND CONCLUSIONS

Etiologic factors and pathogenesis of internal supravesical hernias are discussed with a description of the anatomy of the supravesical fossa.

A review of the nomenclature has shown that at least twenty-two different terms have been used in describing the various types of internal supravesical hernias. ''Supravesical hernia'' has been chosen as the most satisfactory general term for hernias arising in the supravesical fossa. Modifying terms to indicate the origin and location of the various types of supravesical hernias may be used without confusion. Five possible directions of herniation from the supravesical fossa are described and illustrated.

At least 60 cases of internal hernias occurring in the region of the bladder are reviewed and of these 37 have have been reported completely enough to be tabulated as true supravesical hernias. The remainder are considered doubtful cases.

An additional case of internal supravesical hernia of the prevesical type is reported. A preoperative diagnosis of intestinal obstruction of unknown cause was made. The diagnosis was obscured by symptoms of uremia and by lack of typical early x-ray evidence of small bowel obstruction. It is possible that the obstruction was not complete during the patient's first few days in the hospital.

The diagnosis of internal supravesical hernia is possible preoperatively if the symptoms and signs of intestinal obstruction with strangulation, urinary disturbance, and cystoscopic visualization of a protrusion of the anterior bladder are found associated.

The treatment is that of acute intestinal obstruction with strangulation plus simple closure of the hernial sac. The results of treatment depend upon the early recognition of the condition and prompt adequate therapy.

The mortality rate of reported cases has been 44.1 per cent.

We believe that all hernias arising in the supravesical fossa should be called supravesical hernias. The exact type of supravesical hernia may have the additional designation of external or internal. The external type passes either directly through the anterior abdominal wall or indirectly through inguinal, femoral, or obturator openings. The internal type may have prevesical, paravesical, intravesical, or lateral pelvic locations. Hernias extending to the region of the bladder, but arising outside of the supravesical fossa, should be classed according to their points of origin.

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THE USE OF THE RECTUS FASCIA FOR CLOSURE OF THE LOWER OR CRITICAL ANGLE OF THE WOUND IN THE REPAIR OF INGUINAL HERNIA

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SINCE the sixteenth century when Pierre Franco, an ordinary rupture and stone cutter, first relieved incarceration by herniotomy, this operation has been of vital interest to surgeons. However, even earlier references[1] to various operations and other methods employed in the treatment of hernia may be found in the writings of Celsus, Heliodorous, and Paul of Aegina. According to Albert,[1] from the Middle Ages to the introduction of antiseptic surgery various methods have been in vogue and were classified by him as follows: (1) pressure with or without the simultaneous application of irritating and so-called contracting remedies; (2) caustics and the actual cautery; (3) ligature of the sac with or without cutting it off; (4) introduction of foreign bodies into the hernial sac; (5) the injection of irritating fluids within or outside of the hernial sac; (6) subcutaneous suture. Most of these methods are still practiced, and, in spite of the fact that the operative treatment of hernia has been well established for many years, the rebirth of the ancient and discarded method of injection has only recently appeared in the literature. The obvious lack of unanimity of opinion in regard to the operative or nonoperative method of treatment is based upon the fact that in a certain number of patients, although this be a small percentage, operation has failed to bring about a cure of the hernia. There are always, of course, those patients who either refuse to subject themselves to an operation because of fear or who are properly advised against such a course because of some concurrent complications. The most cursory review of the literature will reveal that each year publications on the operative treatment of this affection have been made, thus indicating that, in spite of the fact that the majority of inguinal ruptures are now easily and permanently cured by a variety of procedures and by the average operator, nevertheless, there are a small, but definite, minority of instances in which recurrence is all too common. The underlying surgical principles upon which an operative cure of hernia is based completely baffled the efforts of the best surgeons for years and it was not until the totally independent publications of Halsted[2] and Bassini[3] that the surgical technique was placed on a rational basis. Although after his original contribution in 1890, Bassini made no further reports, Halsted,[2] either directly or through one of his associates, notably Blood-

good[4] and Taylor,[5] constantly reported throughout the years modifications of his operative procedure based on follow-up examinations of patients operated upon according to his method.

In 1903, after fourteen years, the number of patients so operated upon came to over 1,000. It is interesting to speculate not only as to the total number of patients that have had the Halsted operation for the radical cure of hernia performed upon them either by those who were trained on his staff or indirectly trained in his method and technique by one of his former assistants, but also as to the percentage of cures obtained by this procedure.

In one of his later contributions Halsted,[2] after having emphasized the advantage of employing the cremasteric muscle and fascia as well as the possibility of turning back a flap of the aponeurosis over the rectus muscle, as a support to the lower angle of the wound in closing, goes on to state: "The future will decide these nicer points, and it would seem that only the nicer points remain now to interest the operator." It is the purpose of this paper to call attention to one of these "nicer points" or which more appropriately may be called major points that has been found useful not only in the more difficult, but also in the large majority of cases of inguinal hernia; i.e., the employment of the fascia overlying the rectus abdominis muscle in order to close a defect in the lower inguinal region caused by a deficiency of the conjoined tendon.

In the early days of the development of the operation for the cure of inguinal hernia, attention was directed mainly to the spermatic cord and thus to the upper angle of the wound. The cord was felt to be the first cause of the hernia and the main obstacle to its cure. The lower angle of the wound was not considered of as great importance as the upper. Although the truth of the liability of the spermatic cord is not to be doubted, the weakness of the lower inguinal region might be more properly ascribed to developmental defects in the fascia concomitant with the descent of the testis rather than to the presence of the spermatic cord. This point has received support in the now-recognized lack of necessity of transplanting the cord for the successful operative cure of inguinal hernia and has emphasized the importance of proper tissue support of the hernial hiatus in the abdominal wall. As long ago as 1896 recurrences at the lower angle of the wound were recognized by Bloodgood[4] as being frequent, and through the years up to the present time it would seem that Bloodgood's observations have been confirmed; i.e., that the majority of hernias recurred in the lower weak area. One of the most important of the facts ascribed to Bloodgood was the great variation in the width of the conjoined tendon and the responsibility of the insufficient tendon for the recurrences at the lower angle of the wound, through the external ring, directly. In 1892 Wölfler[6] described a method of strengthening this area by using

the lower end of the rectus muscle, but according to his description and the diagram, published by Bloodgood (Fig. 1), the rectus muscle with its fascial covering was drawn laterally under considerable tension and was attached to only the middle third of the inguinal ligament. The inner lower angle, therefore, was not supported by this procedure.

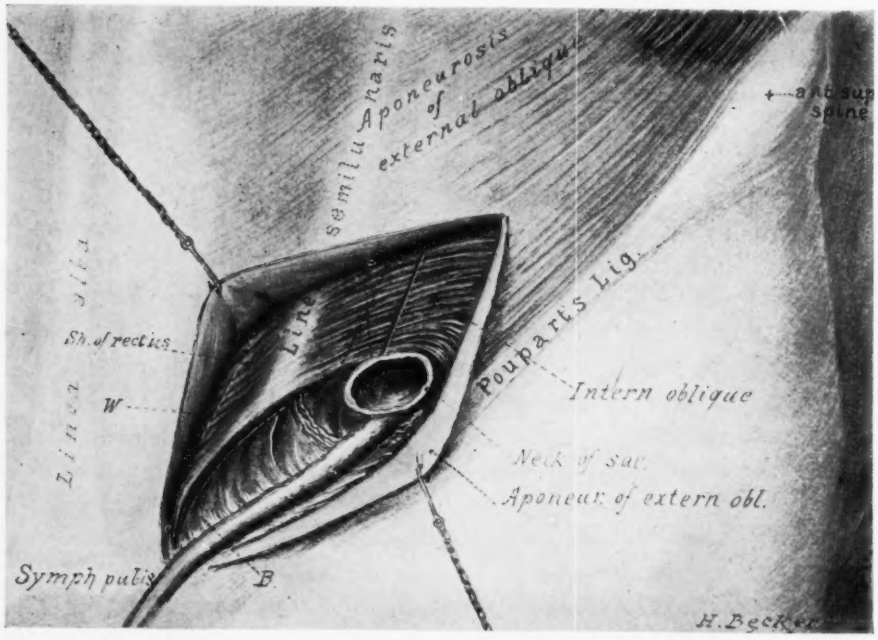

Fig. 1.—The anatomy of the inguinal canal. The straight line on the internal oblique muscle represents the correct direction and extent of its division. The dotted lines represent the direction and position which should be avoided in dividing the muscle. *W*, The direction and extent of the division of the anterior sheath of the rectus in Wölfler's method; *B*, the direction and extent of the division of the fascia to expose the rectus muscle in the writer's method; also, the extent of the conjoined tendon if it is wide and firm; if it is obliterated the transplanted rectus muscle covers this portion of the inguinal canal. (From Bloodgood, J. C.: Operations on 459 Cases of Hernia in the Johns Hopkins Hospital From June, 1889, to January, 1899, Rep. Johns Hopkins Hosp. 7: 223-563, 1899.)

Bloodgood in 1899 also reported the use of the rectus abdominis muscle to fill in the lower angle by incising the lateral margin as shown in Figs. 1-3. This powerful straight muscle gradually pulled away from such a mooring as soon as the patient was up and around. Probably one of the most interesting examples was recently related to me by Follis.[7] He had performed such a plastic closure on a patient who, shortly after discharge from the hospital, was riding a bicycle up Chase Street in Baltimore when he felt something tear in the lower inguinal region. After this incident he greeted Follis with the remark: "This is the first time I have been able to stand up straight since the operation." On examination there was some ecchymosis in the skin near the lower end of the scar. It was assumed that the transplanted portion of the rectus muscle had torn loose. This procedure was finally given up. Berger[8] in 1902 and Halsted[2] in 1903 suggested turning back a flap of the lower end of the fascia covering the

rectus muscle to be used in the presence of a defective conjoined tendon. Fig. 4 is a drawing by Brödel from a sketch made at the time of Halsted's operation by Harvey Cushing.

This procedure of necessity leaves a weak area along the lateral border of the rectus muscle through which herniation has occurred in the past; besides, the flap of the fascia was placed beneath the spermatic cord. Although at times very useful, this method has not been popular. Halsted[2] mentioned relaxation incisions higher up on the rectus muscle in order to loosen the internal oblique so that this muscle might be more readily sewn to a lower level along Poupart's ligament, but he was careful to advise against the employment of relaxation incisions lower down on the rectus because, if it were found desirable to turn back a flap in this region, such incisions might interfere.

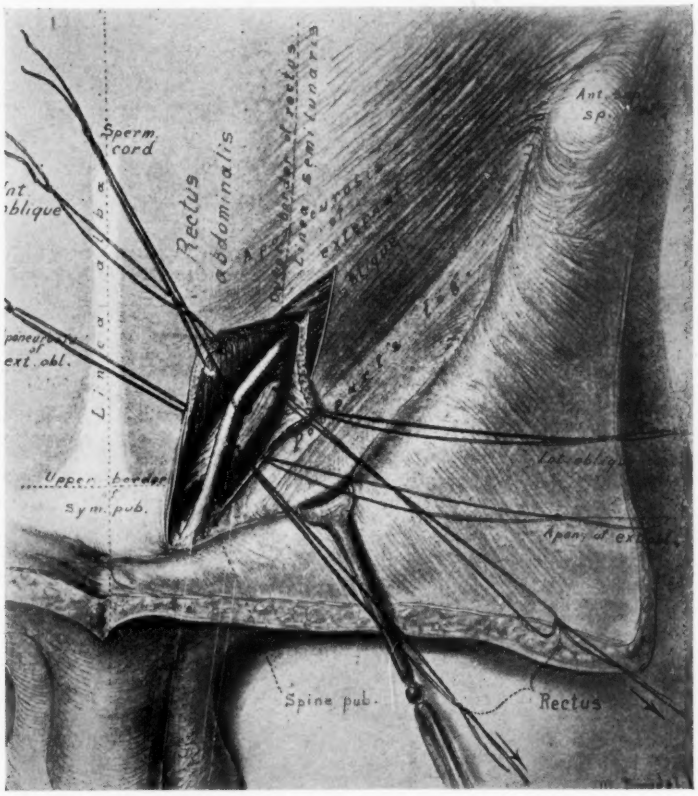

Fig. 2.—The method of transplanting the rectus muscle. The sac has been excised and peritoneal cavity closed; internal oblique muscle has been divided, the rectus exposed and transplanted; at this stage the wound is ready for deep sutures. This drawing shows how perfectly the transplanted rectus muscle lines the lower half of the wound. (From Bloodgood, J. C.: Operations on 459 Cases of Hernia in the Johns Hopkins Hospital From June, 1889, to January, 1899, Rep. Johns Hopkins Hosp. 7: 223-563, 1899.)

Dissections in over 200 cadavers without hernias, performed in the course in surgical anatomy, in addition to experience at the time of operations for hernia called our attention to the fact that the difficulty

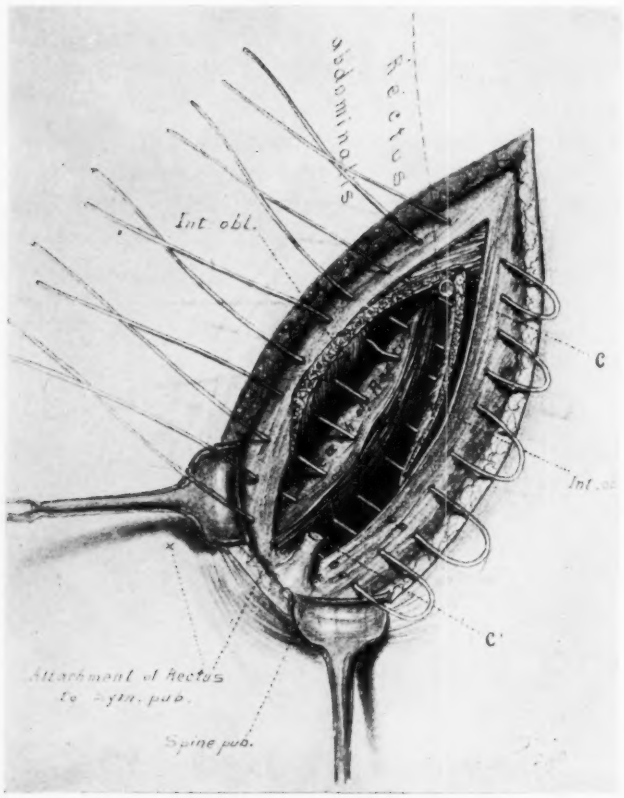

Fig. 3.—The transplanted rectus included by the deep sutures. In this drawing the cord has been excised in order to demonstrate the operation more clearly. (From Bloodgood, J. C.: Operations on 459 Cases of Hernia in the Johns Hopkins Hospital From June, 1889, to January, 1899, Rep. Johns Hopkins Hosp. **7**: 223-563, 1899.)

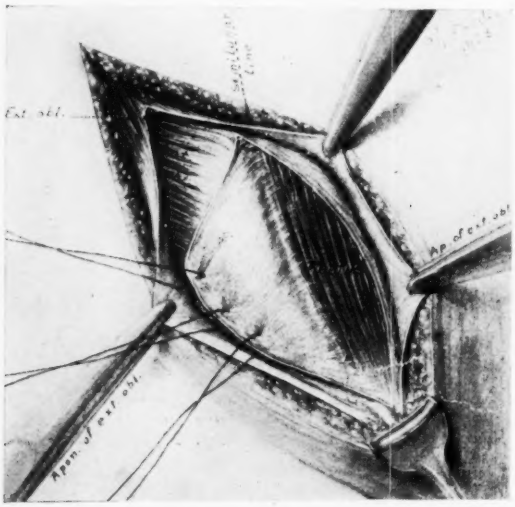

Fig. 4.—Transplantation of triangular flap from anterior sheath of rectus muscle. (From Halsted, W. S.: Bull. Johns Hopkins Hosp. **14**: 208-214, 1903.)

of demonstrating a conjoined tendon or falx inguinalis has been very great indeed. Some of the details of the anatomy of the inguinal region, such as the lateral abdominal muscles and their covering fasciae together with Scarpa's and the transversalis fascia, the aponeurosis of the external oblique, and the inguinal or Poupart's ligament, are well understood, but with regard to other structures the fasciae are quite variable and their relationship indistinct. In a normal, well-developed adult, in the dissecting room, the various fascial layers, even in the absence of a hernia, are almost impossible to demonstrate to the students without producing artefacts. How then can one not experienced in such dissections discover at operation and employ for closure of the hernial orifice these structures that in the presence of a hernia and further attenuation are even more indistinct than normally. The result is, of course, a poor closure of the vital lower angle of the wound with inadequate fascia under more or less tension. The fact that the great majority of recurrences are direct hernias is ample proof of the above statement. In fact, in all but children or very young vigorous adults who are neither fat nor emaciated it is impossible, as a rule, to show in a satisfactory manner any form of fascial layer in the lower inguinal region except the aponeurosis of the external oblique and the transversalis fascia lying next to the peritoneum. Most frequently the surgeon or even the anatomist is confronted with the difficult problem arising from an undeveloped or an acquired atrophy of the conjoined tendon, or from fatty degeneration and atrophy of the internal oblique muscle. Again, even in otherwise well-developed young male adults there is not infrequently a marked congenital attenuation of the entire area between the lateral edge of the rectus muscle and the medial margin of the inner abdominal ring. At this latter point it will be recalled a thickening of the fascia of the internal oblique and transversus fascia is termed the ligament of Hesselbach. The fascial sheet of these two muscles continues inferiorly to contribute to the formation of the inguinal or Poupart's ligament and medially to form a part of the abdominal wall covering the so-called weak area or Hesselbach's triangle. Frequently in the interior abdomen the aponeuroses of the obliquus internus and transversus abdominis remain undivided, lateral to the sheath of the rectus, and this undivided or fused part constitutes the conjoined tendon. Although in the superior part of the abdomen the aponeurosis of the transversus muscle forms the posterior sheath of the rectus, while that of the internal oblique splits to straddle the rectus sheath, these relations are changed in the inferior inguinal region. Inferiorly the aponeurosis of the internal oblique, if it is not fused with that of the transversus to form a conjoined tendon, is inserted upon the ventral surface of the rectus sheath. When strongly developed, it is usually separable at the point of insertion from the transversus abdominis, and

in the absence of a fusion with the latter or of a conjoined tendon, this part of the aponeurosis of the internal oblique forms an aponeurotic arch above with the spermatic cord, the medial part of which constitutes the falx inguinalis. Inferiorly the aponeurosis of the transversus inserts on the lateral border of the rectus sheath when the conjoined tendon is absent. Near the inguinal ligament the internal oblique and transversus abdominis are quite similar in that their muscle fibers arise from the lateral part of the ligament, both having fascial attachment to the ligament throughout its entire length.

In summary, it is very rarely true that a fusion of the aponeurosis of the transversus and obliquus internus, thus forming the conjoined tendon, occurs as far lateral as the internal inguinal ring, and in the average adult it is infrequent that this fusion can be found to occur for any practical distance lateral to the attachment of the conjoined tendon to the lateral edge of the rectus sheath. It is more frequent in the dissecting and operating rooms to find the internal oblique muscle and its aponeurosis the more strongly developed of the two and inserting separately on the ventral sheath of the rectus muscle. The falx inguinalis, in the absence of a conjoined tendon, is usually contributed to mainly by the aponeurosis of the internal oblique. The weakness or strength of the lower inguinal region is therefore in direct proportion to the strength of the aponeurosis of the internal oblique and transversus muscles between the internal inguinal ring and the lateral edge of the rectus sheath. If they are fused, the structure should be termed the conjoined tendon, which may be strong or attenuated in young or old. An accentuation of the lateral portion near the internal inguinal ring has been termed the ligamentum interfoveolare or ligament of Hesselbach, the main function of which appears to be to turn the direction of the spermatic cord. An accentuation of the medial portion has been properly called conjoined tendon, the fibers of which run to the pubis. If the aponeurosis of the internal oblique and transversus muscles are not fused, the conjoined tendon is absent, but the sickle-shaped band of fibers in the accentuated aponeurosis of the internal oblique muscle, the falx inguinalis, however, may be and usually is present and definable. The presence or absence of a conjoined tendon, therefore, has nothing whatever to do with the strength or weakness of the lower inguinal fasciae.

In the adult cadavers and operative cases examined, the internal oblique and transversus muscles together in the great majority of instances have been found to be atrophic, indefinite, and attenuated, rather than definite, strong, and readily demonstrable.

It would appear in an as yet incomplete follow-up of cases operated upon for hernias that the lower inguinal region is probably the most vulnerable point for a recurrence of the hernia, whether primarily direct or indirect hernia, and unquestionably offers the greatest prob-

lem in the satisfactory closure of a hernia wound. For these reasons a simple and most inviting operative method is suggested which not only augments the fascia present in the lower inguinal region, but at the same time permits of a secure closure without producing the slightest tension and thus remains true to one of the greatest and most fundamental surgical principles.

OPERATIVE TECHNIQUE

The operative method and technique employed are in every way similar to those described by Halsted, with the exception of the manner in which the lower angle of the wound is closed. The most meticulous technique and hemostasis are observed and fine silk sutures are employed routinely throughout the wound in bringing about the repair of the defect in the abdominal wall. Transplantation of the spermatic cord has not been done because it is thought to be unnecessary for the cure of inguinal hernia, either direct or indirect. In fact, the cord with its cremasteric muscle and fascia is felt to be a valuable addition of tissue to augment the paucity existing in the lower angle of the wound.

A careful sharp dissection of the hernial sac down to peritoneum, with only the slightest extraperitoneal tissue remaining, is felt to be desirable. Ligation with transfixion sutures of the sac as high up as possible is undoubtedly one of the more important steps in the operation. The stump of the neck of the sac should be allowed to retract freely under the edge of the lower margin of the internal oblique and transversalis muscles. Fixation of this stump to the latter muscles, practiced by some, is to be condemned, for a funnel-like pouch of peritoneum is formed at the site of fixation and may be the starting point of a new hernia. Closure of the neck of the sac, if large, may be equally well accomplished by an internal purse-string suture. On the left side, when a sliding hernia is encountered which interferes with a high dissection of the peritoneum due to the position of the sigmoid colon, a series of external purse-string sutures may be employed to advantage. In this manner the neck of the sac, the area of adjacent peritoneum, and the colon are protruded into the peritoneal cavity by such a series of purse-string sutures laid in a pattern of circles of ever-increasing diameter. Three such sutures are, as a rule, sufficient. High ligation of the sac can be accomplished only if the sac is carefully and completely freed from the tissue surrounding it.

As shown in Fig. 5, the incision is made on an oblique line, beginning about one fingerbreadth inside and below the anterior superior spine of the ilium and crossing down to a point approximately over the external inguinal ring about one fingerbreadth external to the spine of the pubis. A similar incision is made in the aponeurosis of the external oblique muscle along the course of its fibers for the same length as the skin incision. This incision is made so that the external inguinal ring

is divided near its upper middle angle. Care must be exercised in dividing the external inguinal ring not to injure the ilioinguinal nerve. It is for this reason that the ring is divided in its most medial portion. As shown in Fig. 5, the aponeurosis of the external oblique is dissected medially as far as possible from the anterior sheath of the rectus muscle. This dissection is carried well past the linea semilunaris toward the midline, and, depending on the shape of the abdomen, the aponeurosis of the external oblique can easily be freed to within a few centimeters of the linea alba, thus exposing more than the lateral half of the anterior surface of the rectus sheath and its contained muscle.

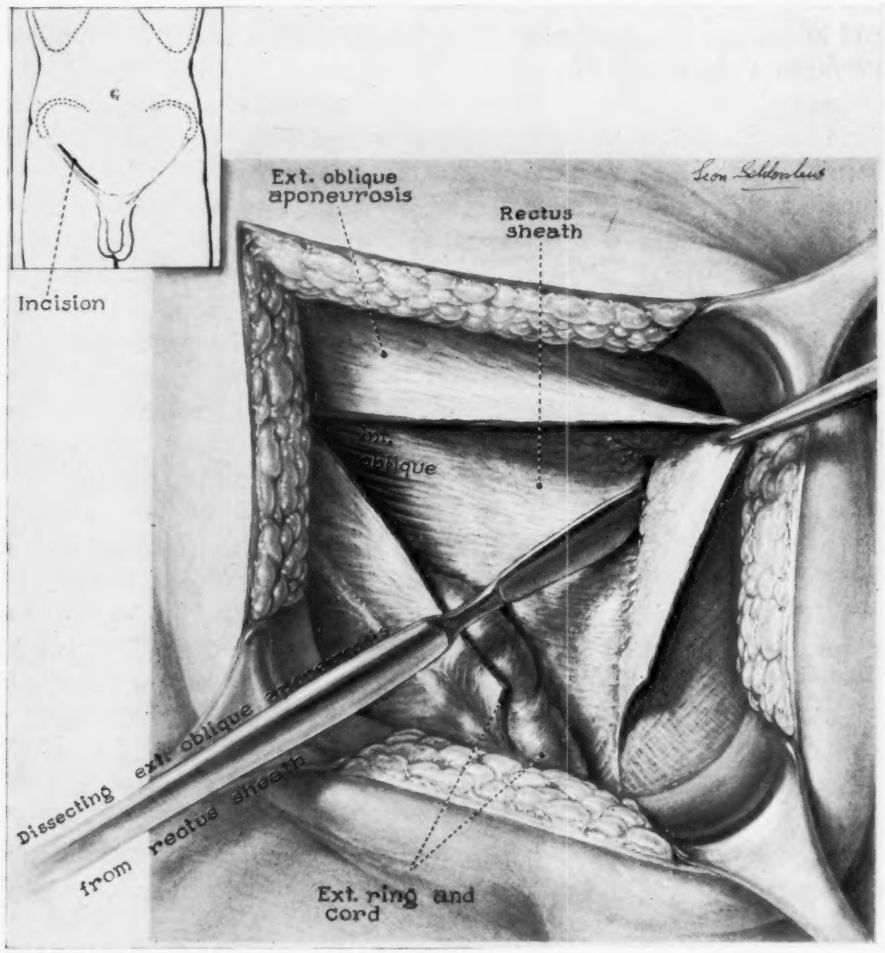

Fig. 5.

A vertical incision is then made through the anterior sheath of the rectus, exposing the pyramidalis muscle and also a portion of the rectus muscle just above its insertion into the pubic bone, posterior to the pyramidalis muscle (Fig. 6). The incision in the rectus sheath is carried down to the superior ramus of the pubic bone and superiorly it may be

continued as far as the reflection of the aponeurosis of the external oblique will permit. This incision releases the anterior sheath and the enclosed muscles tend to bulge immediately. Lateral displacement of the rectus sheath is then accomplished with the greatest ease and closure of the hernial wound is carried out in close accordance with Halsted's technique.

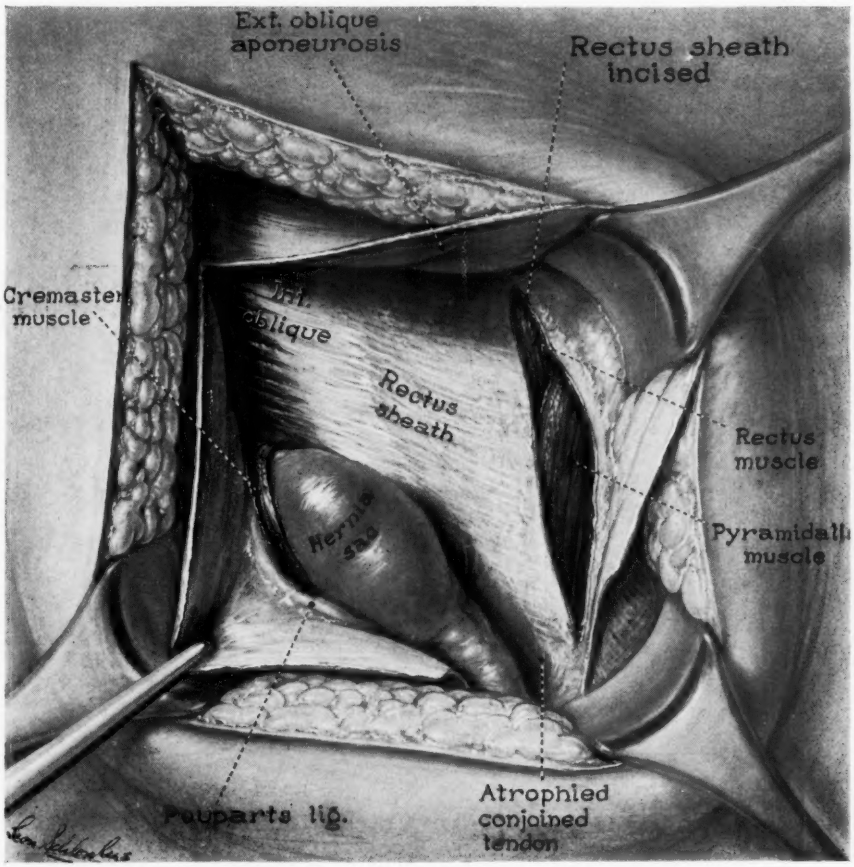

Fig. 6.

As shown in Fig. 7, the cremasteric muscle and fascia are sutured with mattress sutures of fine silk to the undersurface of the lower edge of the internal oblique and transversalis muscles and their aponeuroses, together with the lateral portion of the fascia of the rectus sheath. It will be noted that the spermatic cord is left undisturbed and furthermore that the cremasteric muscle is sutured in such a way that the edge of the aponeurosis of the internal oblique and transversalis muscles, as well as the lateral portion of the rectus sheath, is everted in somewhat of a roll, forming an edge which may be snugly approximated to the inner surface of Poupart's ligament. The cremasteric muscle and fascia not only furnish a strong addition to the tissue closing this

critical angle of the hernial wound, but also serve to obliterate any dead space which might occur after the removal of the hernia.

Fig. 8*A* demonstrates the suturing of this everted edge of the sheath of the rectus and aponeurosis of the internal oblique and transversalis muscles to the inner surface of Poupart's ligament. These sutures consist of interrupted medium C silk, a double one being used for the final stitch. It is likely that fine silk might be used here because, due to the lateral displacement of the rectus sheath, there is absolutely no tension exerted in obtaining the most complete closure of the hernial wound in its superior, as well as in its inferior, portion. The lower sutures take in not only the lateral margins of the sheath of the rectus, but also whatever other fascia is present in the form of either conjoined tendon, or remnants of it, as well as the falx inguinalis in the event the conjoined tendon is absent.

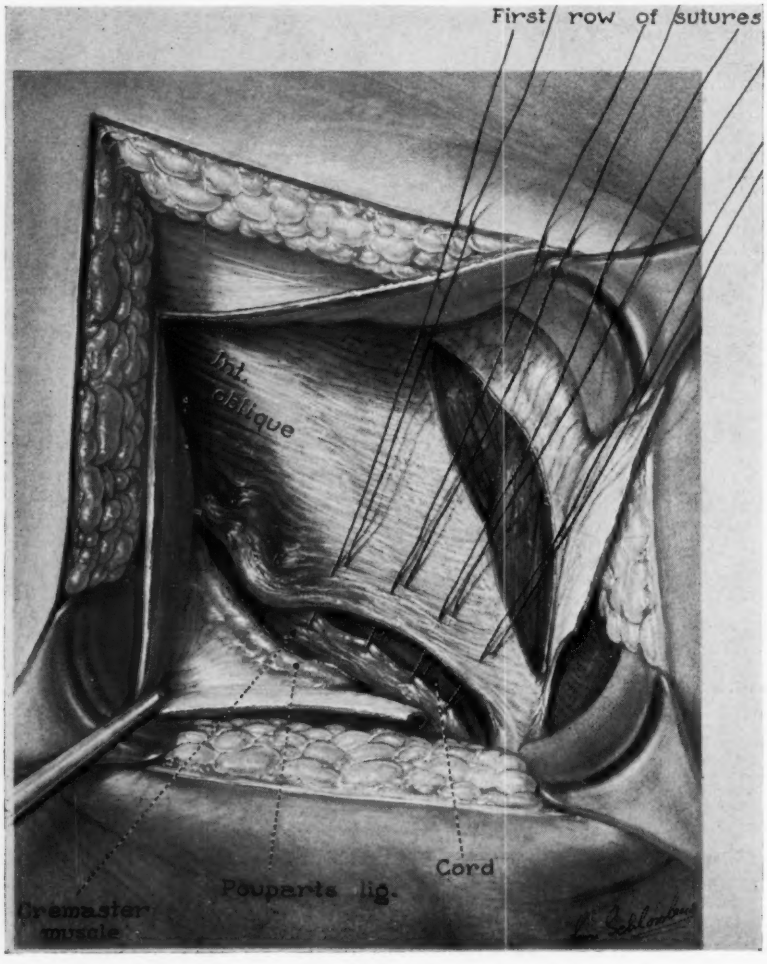

Fig. 7.

Fig. 8*B* represents the sutures shown in Fig. 8*A* tied, as well as the sutures holding the cremasteric muscle and fascia. The facility and

effectiveness of the closure when the anterior sheath of the rectus muscle is incised and displaced laterally is quite striking. The hiatus in the anterior sheath is rapidly reformed by the growth of the fascia. The disagreeable features associated with turning out a flap of the rectus muscle are thus avoided for there is no resulting weakness at the lateral edge of the rectus nor is there any permanent defect in the

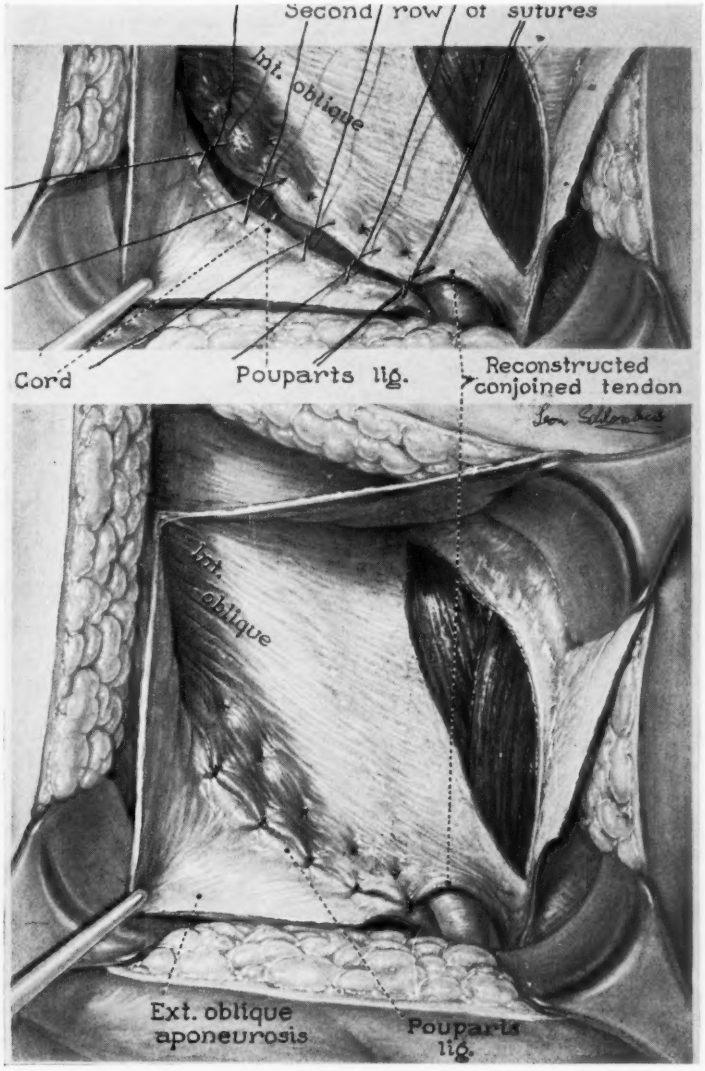

Fig. 8.

sheath of the rectus. A most secure closure of the lower critical angle is thus obtained in the simplest manner and one that is now routinely employed in all inguinal hernias, regardless of the degree of conjoined tendon present or the amount of fascia in this region, rather inadequately described as the weak area, the triangle of Hesselbach, or the lower angle of the wound.

The overlapping of the middle and lateral flaps of the aponeurosis of the external oblique is then accomplished, as shown in Fig. 9*A* and *B*. Interrupted mattress sutures of fine silk are so placed that the lateral flap is tacked to the inner surface of the middle flap and the edge of the middle flap is then sewn down to the anterior surface of the lateral flap. This imbrocation of the aponeurosis of the internal oblique not only

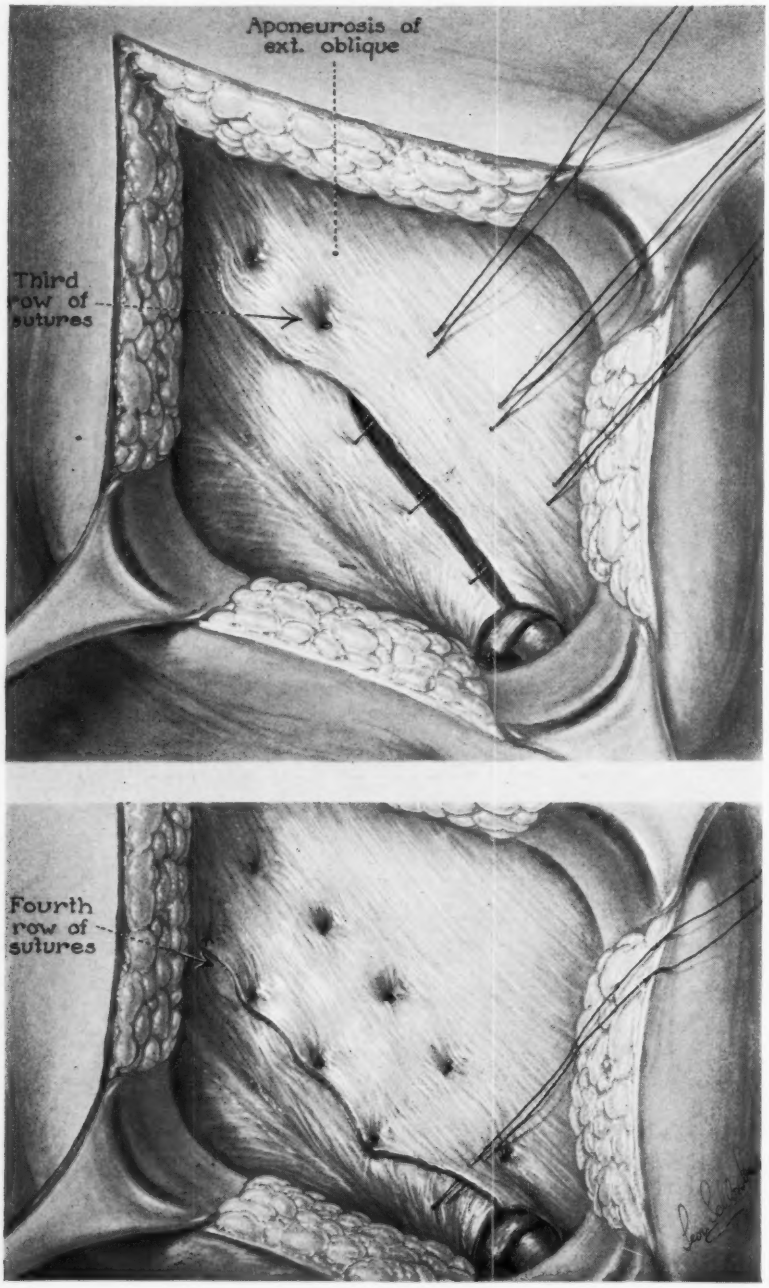

Fig. 9.

forms a stronger abdominal wall than would occur in the mere apposition of the incised edges, but also permits of a broader approximation of surfaces and thus more secure healing. Scarpa's fascia is then brought together with interrupted fine silk sutures and the skin is closed in a similar manner.

There do not seem to be any objectionable features to this procedure and it is of the greatest comfort to the operator to be able in a simple but efficacious manner to employ such an inviting and natural procedure. The question of any tension is immediately done away with in the closure of the fascia over the lower angle. In this manner it is felt that the percentage of recurrences of a hernia in the lower angle of the wound will be very much reduced.

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CURRENT TREATMENT OF CANCER OF THE LIP

A Clinical Speculation

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AN UNDERSTANDING surgeon never thinks of squamous-cell or adenomatous cancer as disassociated from potential lymphatic metastasis, and we are finding that even presumed or proved basal cell growths are not necessarily above suspicion (Figs. 1-3). The supposedly relative infrequency of gland involvement from squamous-lip cancer is of itself no sufficient warrant for ignoring its possible occurrence in any individual case. The old surgical estimate was that 70 per cent of squamous-cell epitheliomas of the lip are cured by any type of local treatment that completely controls the primary focus. It is possible that, if the men who are content to treat only the primary lip lesion were able to follow the majority of these patients for a period of five or ten years, the above percentage of lymphatic immunity might prove to be reduced materially. Right or wrong, many present-day radiotherapists decry prophylactic cervical gland dissection as being unnecessary or even harmful after proper radiation of the primary lip growth. This is a vital issue and it might help to clarify the discussion or speculation if the known and unknown factors which their premise must compass be here marshalled and discussed in one group.

There can be no question of a cancer-free interval of varying length between maturity of a primary squamous epithelioma and the occurrence of regional gland contamination, and, if within this absolutely gland-free interval the primary growth were destroyed, the patient will have been cured without surgical invasion of the neck. However, at present we have no way of recognizing just when gland contamination, which is the termination of the free interval, does actually take place. The first clinical characteristic of lymphatic gland metastasis is enlargement of a node, but of necessity there must have been a further lapse of time between contamination of the node and its becoming palpable. This second period, antedating recognizable metastasis, for all we know might be very brief, but from occasional instances of late cervical metastases developing long after destruction of the primary lesion we must conclude that the quiescent period can be prolonged indefinitely, the cancer material apparently remaining dormant within the node for months or years. In cases of this type under our own observation the quiescent period has varied from several months to thirteen years (Figs. 4 and 5). This is not a new observation: Butlin, some thirty-five or forty years ago, recorded similar behavior of the nodes following tongue amputations. Treves cites certain deep squamous-cell neck cancers which he regarded as arising from branchial cleft rests. Our first case of the kind came to us about thirty years ago and in almost all cases we have

been able to find at least a scar and a bit of history strongly suggestive of a cured epithelioma.

In the foregoing, in the event that we have overlooked some essential modifying element belonging to the above problem, it might be helpful if those denying the propriety of prophylactic gland removal after destruction of even a high-grade lip cancer would publish more generous

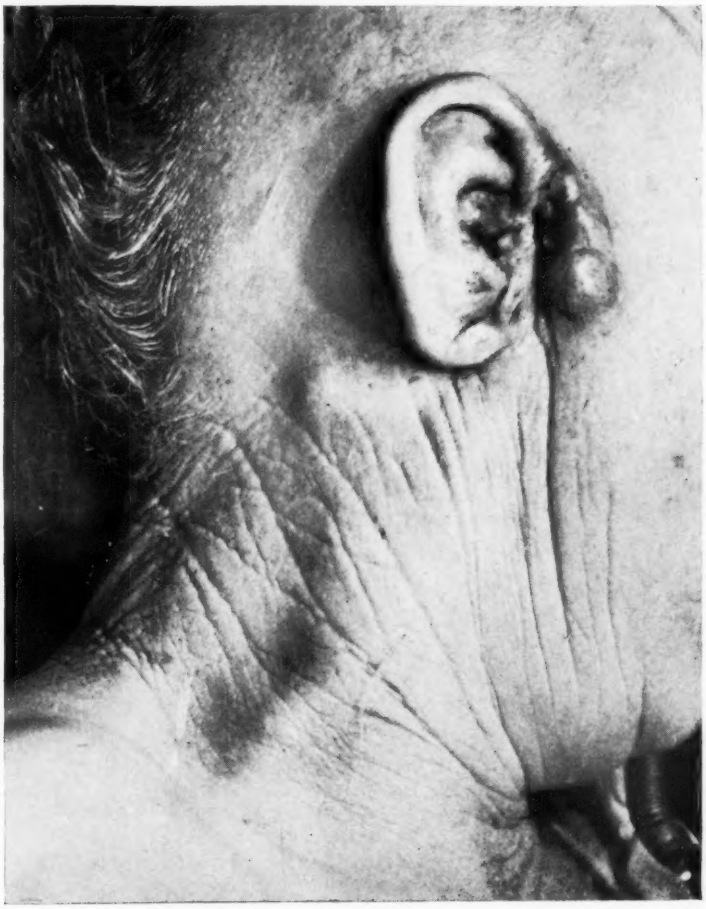


Fig. 1.—Illustrating squamous-cell node metastases from a basal cell primary growth. *History:* Patient aged 68 years. The ear canal lesion had been growing slowly for several years and patient was referred for treatment because of some recent hemorrhages. *Findings:* This patient had an ulcerated, clinically and microscopically, basal-cell primary growth in and about the ear canal, with a large mass of typical, microscopically positive squamous metastases to the glands in the upper neck. *Treatment:* Complete right-side neck dissection and deep destruction of the primary growth and underlying bone by cherry hot soldering irons.

records of five-year follow-ups and microscopic findings upon which convincing conclusions might be based. This is not meant as a challenge but simply a request for information to which we have not had satisfactory access. We personally see too few early lip cancers to make our results of any statistical value, but, whether few or many, their usually slow onset and insignificant appearance in that stage often fail to impress the patient and this makes a post-treatment follow-up more difficult than in other mouth epitheliomas.

Disregarding the comparative intrinsic value of radiation versus excision or mass destruction in the treatment of early or moderately advanced squamous epitheliomas of the lower lip, present public opinion gives a better break to radiation than to surgery on the time-of-treatment factor, and this is the greatest advantage that could be asked. The average patient seeking treatment by a regular medical practitioner is much more apt to choose radiation, which conforms to the widely publicized slogan, treatment or cure "without knife or cautery," than he is to have a sizable piece cut or burned from his own precious lip.

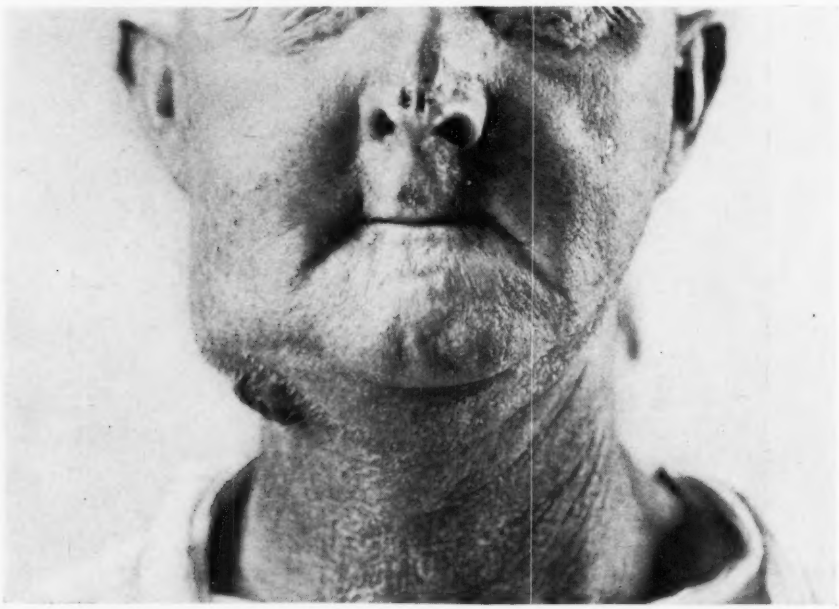


Fig. 2.—Illustrating cervical node involvement from a chronic skin ulceration on the nose. *History:* For several years the patient had a "sore" which was described as an ulceration, not as a wart, on the nose, and about a year before our examination he had noticed the submaxillary enlargement which continued to grow. A few months after this node enlargement, the nose lesion was destroyed with "caustic." *Findings:* The nose lesion had healed with scarring and two perforations through the alar cart 'ages. A fixed mass of ulcerating glands in the submaxillary region was clinically an microscopically squamous-cell cancer.

Therefore, wisely used radiation has the better chance of eliminating the primary growth before cancer material overcomes the node's resistance than has local surgery. From the strides radiotherapy has made in the past two decades, it seems not unreasonable to hope that sooner or later this or some other selective agent may ultimately supersede mass destruction of even cancerous lymph nodes—"A consummation devoutly to be wished"—but we must deal with present facilities.

Granted positive instances in which a contaminated node has retarded metastases for several years, can we deny either that the nodes in any treated case might have already been contaminated or that there can be unrecognized instances in which the invaded gland totally destroys the contamination? If the latter does happen, it but increases the uncertainty as to how often or how early a purely transient gland contamination actually does occur.

Repeated careful examination for the discovery of enlarging nodes of a suspicious feel is not always a safe substitute for removal of possibly contaminated nodes, though at times we all resort to it. Patients will ordinarily return at stated intervals but not for very long, and most of those who do so regularly are driven by peace-destroying fear. In tongue cancer we have seen doubtful nodes enlarge and become inoperable during a five-week interim between two observation visits.

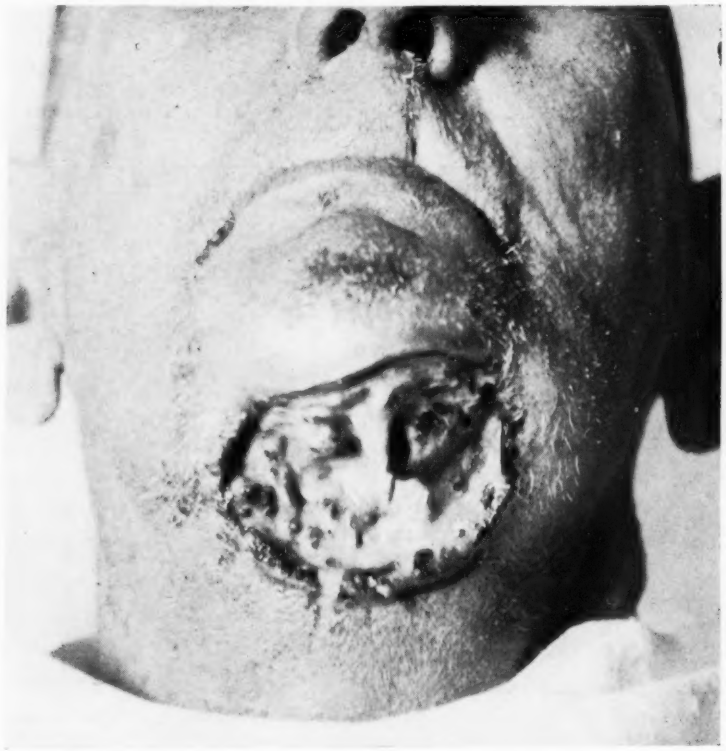


Fig. 3.—Illustrating x-ray-cured lip ulcer followed by metastases which subsequent x-ray failed to control. *History:* Patient 68 years of age. One year previously he had an ulcer on upper lip which was controlled by x-ray. Four months later there began a breakdown in the submental and submaxillary regions. *Findings:* Induration and open ulceration of the submental and left submaxillary regions. Epitheliomas of the upper lip are rare and, when they do occur, are prevalently regarded as basal cell and therefore not apt to metastasize to the lymph nodes; however, true squamous-cell carcinomas do occur on the vermilion or its border and should be treated as such.

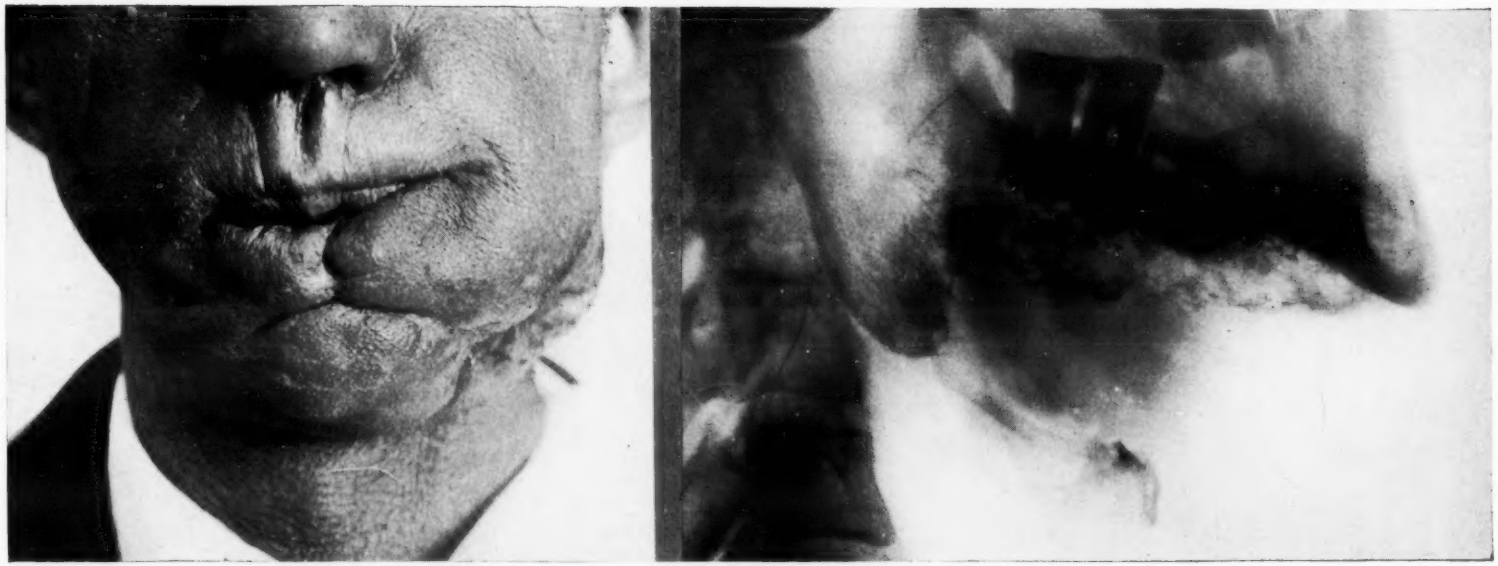
While mass or selective radiation of the glands of the unopened neck has not been our procedure of choice, the fractionated method as originated by Coutard is unquestionably helpful in postponing the final outcome of inoperable involvements.* Though there are no statistics

*In a personal communication Sherwood Moore, Director of the Mallinckrodt Institute of Radiology of Washington University, St. Louis, expressed himself as follows: "It is my personal opinion that the suffering of the patient from prolonged fractionated x-radiation of metastatic glands in the neck is far greater than the suffering from surgical excision. The mortality rate is higher in the latter than in the former, on the average, but with skilled surgery I think the mortality rate would be about even. Radiation of an intensity to insure results has caused constitutional ill-effects on the patient. There may have been cases of cervical gland metastasis treated by radiation that recovered, but offhand I cannot recall an example of it in my own experience."

suggesting that it is as effective as an early, properly performed excision, there are many circumstances which can render x-radiation the more appropriate, dictated by the stage of the disease, the condition of the patient, or his wishes. However, neither logic nor clinical experience justifies certain recommended unsurgical diagnostic procedures that risk crippling gland resistance without compensatory gain for the patient. Negative findings from suction needling or the use of a punch on a suspected gland are not of sufficient weight to warrant the employment of either; positive ones only confirm what we at present prefer to take for granted. Biopsies are not often necessary for diagnosing any but very early lip lesions, but we use them rather routinely for checking both the diagnosis and the grading of the primary lesion, per-

Fig. 4.—Illustrating squamous-cell buccal node metastasis years after the control of a lip epithelioma. *History:* Patient 76 years of age. Eleven years previously a "cancer" on the lower right lip had been controlled with surface radium. He has had recent right submaxillary growth and ulceration. *Findings:* Patient had keratotic skin on hands and face and showed a well-healed lip scar. He had a fungating mass approximately 4 by 5 cm. on right lower cheek and submaxillary with deep induration, but roentgenogram did not show bone erosion. The buccal gland was enlarged but no lower glands were felt. *Treatment:* Under deep block anesthesia, twelve 12.5 mg. needles and two 10 mg. needles of radium were implanted in various places in and around the area, giving a total dose of 2,730 mg. hr. Death occurred ten months later. Growth was not controlled.

forming a biopsy of a gland only when the suspected original lesion has been previously eliminated. The proper interpretation of the biopsy picture is most important. A positive diagnosis of epithelial malignancy in all probability will be correct, but a negative microscopic diagnosis that controverts a positive clinical picture of cancer should be regarded with at least grave suspicion. We have long been of the belief that under the above circumstances, in the final analysis, the patient should be given the benefit of the doubt by treating the condition as cancer. We, ourselves, have had few occasions to make such a decision because usually a recheck or another specimen has settled the matter, but we



A. *B.*

Fig. 5.—Illustrating either dormant sequestration of cancer material or retarded development of a true metastasis within a cervical node, coming from a lip epithelioma. *History:* A 38-year-old plumber burned the lower lip with a splash of hot lead. The wound was indolent for a year, then healed after use of caustic; radium was applied to an "abscess" three years later. *Findings:* Two years after the radium treatment fissure perforation occurred across lower lip with rough borders. He had at this time a hard right buccal or submaxillary node. *Treatment:* Wide excision of borders of lip perforation and repair with sliding cheek flaps was performed. Neck dissection was advised, but this was not permitted. *Later Findings:* Patient did not return until eight years later, when he had a wide involvement of the submaxillary nodes, cheek, and mandible of that side. There was no lip recurrence, but active submaxillary growth had been noticed some months previously.

A shows the healed lip and recently appearing neck and cheek ulceration, taken eight years after excision of radiation scar and repair of the lip.

B shows the type of cancer destruction of the mandible which we have found typical of an extension to the bone from a buccal or submaxillary lymph node. On the postoperative microscopic examination the tissue from the rough borders of the treated lip fissure were reported "inflammation," but on re-examination it was found to contain squamous cancer. The gland and cheek tissue removed eight years later was also squamous-cell cancer.

have seen many cases in which, from the history and the description of the mouth lesion, we felt a positive diagnosis should have been made without hesitation on the clinical picture alone, but which had been allowed to become far advanced or inoperable because of that rather stereotyped laboratory return of "no cancer found" (Fig. 6). The finding of pus in a suspected neck does not of itself eliminate the possibility of cancer being present.

The majority of incurable lip cancers which we have observed were such because of cervical metastases rather than from spread by continuity, and in some of these the primary lesion had already been completely controlled.

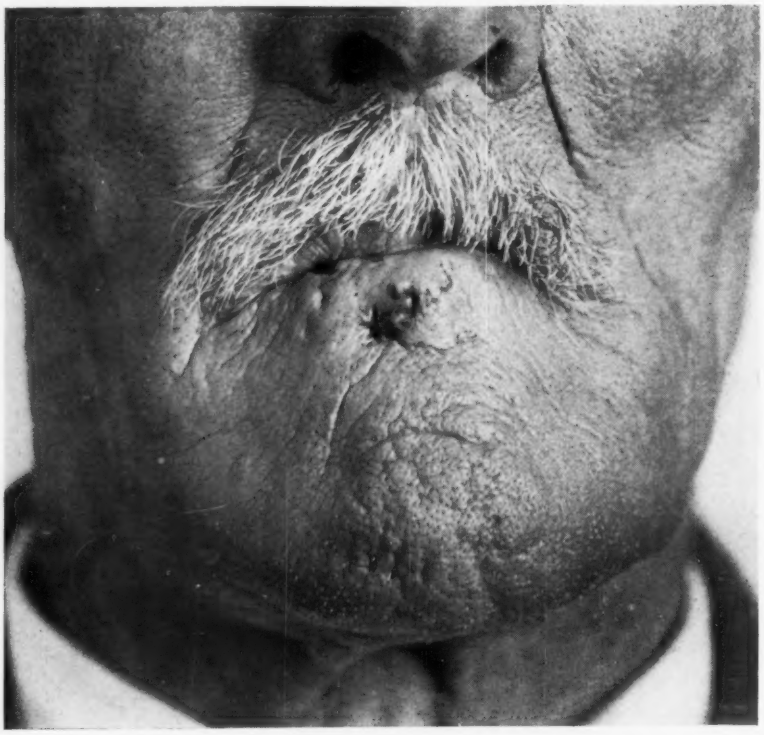


Fig. 6.—Illustrating ingrowing types of epitheliomas. *History:* Patient aged 65 years. He had a sore on lip for eighteen months which had received a great deal of radiation. *Findings:* Induration of practically the whole lower lip with a nodular fissure; loss of beard and glazed skin from radiation; hard nodes in both sides of neck. *Treatment:* Block excision of entire lower and part of upper lip, suturing mucosa to skin. Complete right-sided neck dissection. Dissection of left side postponed because the removed glands were reported negative. *Microscopic examination* of lip showed squamous-cell carcinoma. Right nodes were reported microscopically negative, and the patient did not return for the left-side neck dissection. We were informed by letter that the patient died one year later, and that "the neck lumps had come through the skin and caused hemorrhage." The pathologist had failed to identify cancer in the nodes of the right side, but the clinical picture and subsequent outcome were both typical of cervical node metastasis.

RECAPITULATION

Too often in the recent past more attention has been focused on simplified treatment of the primary lesion than upon the cure of the patient. The greatest assurance of both, in the simplest fashion, can be accomplished by:

1. Early removal and microscopic examination of all possibly precancerous lesions or a cautery-biopsy examination of the more advanced. The first will prevent many cancers; the latter will be of great help in planning treatment of the case in hand.

2. Proper attention to possible involvement of the cervical lymphatics.

3. Mindfulness of the fact that death from cancer of the lip or mouth is one of the most terrible ordeals to which human flesh is heir.

There are five accepted facts upon which the intelligent surgical treatment of epithelial cancer is based:

1. If the cancer is completely removed before dissemination occurs, the patient is cured as far as this particular growth is concerned, but this does not eliminate the possibility of the development of some other independent focus.

2. Metastasis occurs chiefly through the lymphatic vessels to the related lymph nodes.

3. The lymph nodes are agencies of resistance against cancer dissemination.

4. The earlier the primary growth is eliminated, the less likelihood of demonstrable lymph node involvement.

5. Even if a limited number of these do become grossly involved, the disease might still be controllable.

It is unfortunate that inferential, if not plain spoken, doubt as to the possibility of controlling demonstrably cancerous nodes by proper surgical removal frequently emanates from accepted "authorities" based chiefly upon their own lack of personal experience or lack of observation of the work of men accustomed to do this kind of surgery. That a worth-while percentage of these cases can be salvaged, even those with palpable nodes, is proved by the experience of many surgeons of unquestioned standing who have followed the teachings of Butlin, Roux, Crile, Kocher, etc., the combined published statistics from all these being of sufficient volume and detail to be irrefutable.*

Many radiotherapists have criticized mass cervical node excision, prophylactic or therapeutic, on the ground of its supposedly high essential mortality, citing in proof of this statistics of operations done

*In a series of 70 of our own cases treated before October, 1928, that were so far advanced as to require the combined operation of removing lymph nodes and primary growth at the same sitting, there were 16 cures of from five to eighteen years (22.86 per cent). In 29 of the 70 cases the glands were apparently negative, with cures of 20.6 per cent; while in 41 cases the glands were definitely positive, with 10 cures (24.5 per cent). For the whole series there were 23 per cent cures and a 34 per cent postoperative death rate. Our average of five-year-plus cures for the two-step operation for the same previous-to-1930 period was 46 per cent with a 5 per cent postoperative death rate. (See Blair and Brown.[1])

For the subsequent series cared for before 1932, we had 11 mouth cancers with complete operation in one step, with 36.6 per cent living five or more years and 11 cases operated upon in two stages with 55 per cent living five or more years. In this second series there were no postoperative deaths for the two-step operation and 18 per cent for the one-step operation. The lessened operative mortality of the latter series was due to almost no radical change in the operative procedure and to improvement of the organization of our house service and to the elimination of a group of cases that in the first series had given a 45 per cent mortality with no cases living five years later. Of those in the earlier group having a complete one-step operation, 1 out of each 5 died before complete postoperative recovery and a 33 per cent chance for a five-year-plus cure, while of those in the later group 1 out of each 11 died postoperatively and 49 per cent plus had five-year-plus cures. (See Blair, Brown, and Byars.[2])

for control of true mouth cancers which in different operative series of our own cases, as cited above, has varied from 0 to 45 per cent, depending chiefly upon the stage of advancement of the cases. Large or small, however, this death rate has no real bearing on that to be expected from neck dissections done for early lip cancers. As previously stated, we see too few of the latter to present real statistical value, but, based on some observation of the latter cases, we feel that prophylactic upper neck dissection for early cases should be about as free from mortality as any major operation in surgery. That there might be an essential mortality percentage following complete neck dissections done for advanced gland involvement from a high grade lip cancer is a self-evident fact, but untreated the death rate of such cases is just about 100 per cent; until radiotherapy can present satisfactory statistical evidence of a reasonable percentage of five-year-plus control for these advanced cases, even a 10 per cent mortality from well-planned surgical attempts would be open to criticism, chiefly because every operative death tends to prevent future sufferers from seeking indicated surgery at a stage of the disease when surgery would have a fair chance of being both helpful and free from danger. Quick voices the sentiments of Edwards,[3] Martin, and many other radiologists when he states that because "a healthy lymph node can digest and destroy tumor emboli . . . therefore the lymph nodes should not be excised." But how are we to be sure that the lymph nodes in the particular case still remained healthy?

Though it is generally accepted that lymphatic metastasis results from the passage of some sort of cancer material from a primary lesion through a lymph channel to lodge in a node, (a) how and (b) when is node contamination hastened or retarded and (c) what factors hasten or retard it, and what initiates the change from dormant contamination to actual demonstrable metastatic growth within the node? The answers to these questions all still remain matters for interesting, if not profitable, speculation. From neither the clinical characteristics nor the microscopic picture can we make more than a guess as to how early or how late the individual primary lip, mouth, or face cancer will cause cervical gland metastasis or whether or not it will ever occur.

1. We assume that cancer material or a cancer cell breaking free from the parent growth is carried to the gland through a lymph channel, but few, if any, microscopists have ever actually recognized either the exfoliation, the passage of the cancer material through the lymph vessel, or the early characteristics of the cancer material that has already found lodgment within a node (Fig. 6); and, unless we can grant to either the lymphatic vessels or the newly divided neck tissues a faculty of destroying cancer, the second and third of our previously cited "accepted facts" are both apparently somewhat unreconcilable with Butlin's successful practice of removing the glands en masse ten days or two weeks before performing the tongue amputation.[4]

2. As already cited, we apparently can have no knowledge of the exact time of gland contamination.

3. It is a modern teaching that a moderate amount of radiation to the gland area may prevent or delay the development of metastases, but as far as we know this is not proved and certain of our own experiences have suggested the possibility that partial irradiation of the nodes incidental to the treatment of the primary growth might on the contrary stimulate the metastatic growth; we have modified some of our technical procedures to anticipate this possibility. Certain clinical observations suggest that trauma can hasten the glandular metastasis, and we have seen several such instances.

It is well known that certain epitheliomas of more or less distinct clinical characteristics and of somewhat corresponding histology are more apt to, and on the average will more quickly, cause gland metastasis than will certain others, and this fact is with propriety often taken into consideration in making a tentative estimate of the likelihood of present or future gland metastases in the individual case. However, in making this estimate, as a rule, most have failed to credit the gland function with any active power to kill cancer cells, apparently regarding the latter as a sort of static, somewhat like that of the trap under the pantry sink. However, there are several clinical observations bespeaking the contrary. One is the dormant period already cited. Another is the long periods of time that an active metastasis can develop and increase in one node without demonstrable invasion of any neighbor, while less frequently a whole mass of related glands will enlarge almost simultaneously, this latter sometimes following an injury. Another example of special resistance is the great rarity with which epithelial cancer arising in the face or mouth ever will metastasize below the clavicle. With the exception of an occasional axillary node enlargement, in all but two of the few cases we have seen of generalized metastases from face or mouth, the first recognized symptoms have been of liver involvement, ascites, etc. The mechanism or chemistry which sustains this special protection might not differ in essence from that guarding our whole organism, but it has a special significance with supraclavicular cancer, for in the vast majority of cases total elimination of the latter would amount to a cure, free from the danger of distant recurrence.

This behavior of the nodes might suggest the presence of some material that gives to the gland an active but variable resistance against the development of cancer emboli.

Be this as it may, until the above or some other type of biologic control is given us, our present function still remains the early recognition and destruction of the primary lesion with due regard for possible or probable present or future metastases. It stands to reason that the more acceptable the remedy, the earlier will be the average time of treatment, but acceptability should not be allowed to compromise

efficiency. Radiation is the most generally acceptable, and when properly done it has a high average of efficiency in controlling the primary lip lesion, but we have not found this true in regard to the lymph nodes.

That the average treatment does not truly reflect the potential efficiency of present-day medicine for the control of this disease is suggested by the fact that we still see a rather small percentage of early lip, face, and mouth cancers, most of them having previously been observed or subjected to some essentially inadequate plan of treatment.

Fig. 7.—Illustrating a large, rapidly "outgrowing," cauliflower mass, clinically of low malignancy. *History:* Patient aged 75 years. He had a wart on left lower lip for many years and three years previous to our examination had consulted a physician who gave him "treatments" and applied paste. The lesion continued to increase in size and became dry and cracked. *Findings:* A large cauliflower mass, shown in illustration was present, but without ulceration and no node involvement mentioned. *Treatment:* Destruction with soldering iron cautery was performed and a repair was made from forehead flaps. The neck was not opened. *Result:* Six years later, at the age of 81 years, he had a severe fall, with fractured ribs. The patient was in poor condition, but without sign of recurrence. He died shortly after this. *Microscopic examination:* Squamous-cell carcinoma.

In some, if not the majority of, instances this has not been due entirely to the victim's own negligence. The past and present concentrated efforts of certain in our profession plus those of the public health, social, and educational agencies to make the public cancer-conscious have not been wasted as far as the laity is concerned. Nor can the physician

previously consulted be justly held entirely responsible for faulty advice or the inadequate treatment given. Lip and mouth cancers are not of common occurrence and the average practitioner is seldom a special student of these lesions; therefore he must look to higher "authority" for guidance. When he finds the accredited teachers apparently divided in their expressions, it is but natural that he should attempt to carry out his own interpretation of what he takes to be the simplest plan presented, but possibly without any real understanding of what was meant or what is needed for its execution.

It is comparatively simple to state underlying principles of any plan of cancer treatment, but, owing to the varying conditions that must be met in actual practice, their successful application will depend as much

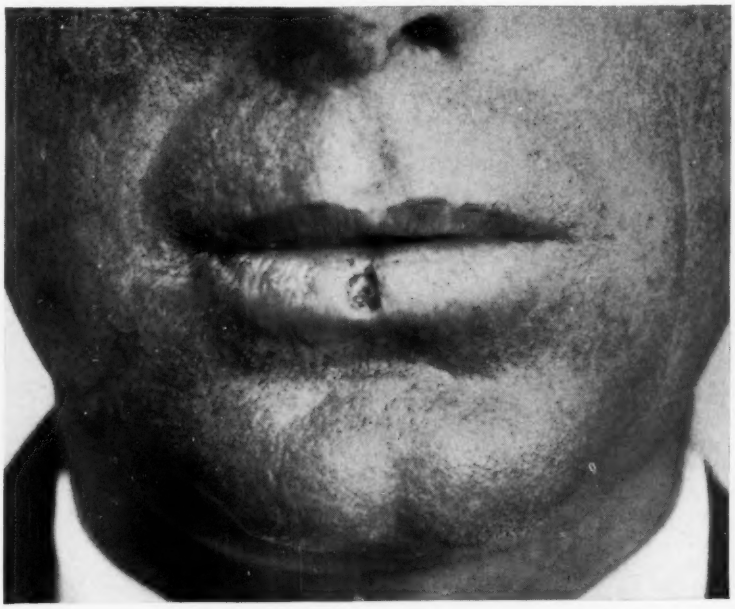


Fig. 8.—Illustrating the "ingrowing" type of epithelioma. *History:* Patient aged 26 years. He has had a central lip fissure for a year which is now enlarging laterally. *Findings:* Patient had a small "scooped-out" ulcer with slight induration. *Treatment:* Biopsy of lip ulcer was performed, followed by radium and later upper-neck gland excision of both sides. *Microscopic examinations* of lip and glands both showed squamous-cell carcinoma.

upon the subconscious judgment that comes from long intelligent observation as upon any rule-of-thumb. Somehow one gets the impression that certain writers, in their efforts to simplify and at the same time broaden the scope of the latter, have occasionally tricked themselves into advocating practices they would not, or should not, always follow. We should never lose sight of the accepted principles upon which our plan of treatment is based, nor the fact that each individual lip cancer is an individual problem. The plan for its proper treatment may be influenced or modified by any number of factors: the age and condition of the patient, the kind and number of previous treatments, the duration of the lesion, the rate of growth or a change in rate, the presence,

absence, or character of node enlargement, and the physical characteristics of the primary lesion; these and others all must be considered. For instance, it is an old and long-accepted observation, which can now be classed as knowledge, that the mere size of the primary lesion means little, but the direction in which it grows is of the greatest significance. When the latter is outward, away from the surface, intensity of its virulence may be in inverse ratio to its size (Fig. 7) but with growths and ulcerations that invade the underlying tissues (Fig. 8) the seriousness of the case is apt to be in indirect proportion to the size and depth of the invasion. Some very minute or undiscovered ulcers can cause widespread gland involvement, while other huge masses may show no cancer in the related lymphatics.

Microscopic grading does give positive evidence of malignancy to the extent of its positive findings, but does not exclude the presence of an unrevealed area of a higher grade than that actually observed. On the other hand, the microscopic lip picture should be rated maybe as much as two degrees less virulent than the same picture found in a tongue lesion, but there is no warrant for ever permitting high microscopic grading alone to deprive the patient of the chance of control that might come from wide excision or a well-performed neck dissection. Can the general practitioner who usually first sees these cases be expected to compass all of the above and more from a few trite rules based often upon a large series of cases but possibly questionable follow-ups and which he may find contradicted in the next article he reads on the subject?

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ARTERIOSCLEROSIS IN PANCREATIC DIABETES*†

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THE extensive literature on arteriosclerosis has been recently collected in a book[1] published under the auspices of the Josiah Macy, Jr., Foundation, and will not be reviewed here. A consideration of this literature indicates that, whereas much significant information has been obtained, the pathogenesis of this disease remains obscure. As pointed out by Wells[2] the fact seems undeniable that the arterial colloids, like those elsewhere in living tissue, undergo definite changes with age, leading to their progressive dehydration and loss of elasticity, and that these changes in the arterial walls in time must result in gradual dilatation and elongation of the vessel. However, the development of atheromatous lesions in the intimal layers with calcification does not take place in the arteries of all old people and there is some basis for the view that some of these changes are not inevitable but may be due to some metabolic defect. The experimental production of atherosclerosis in the aortae of rabbits by the feeding of cholesterol, as in the experiments of Anitschkow,[3] Leary,[4] and others, furnishes strong support for this view. Leary has presented convincing evidence with respect to the similarity between these experimental lesions and atherosclerosis in man.

The abnormally high incidence of presenile arteriosclerosis in diabetes mellitus has been generally recognized. Joslin[5] and his associates in particular have called attention to this complication and it has recently been commented upon by a number of observers (Morrison and Bogan, 1929,[6] Rabinowitch, 1935,[7] Hallock, 1936,[8] Ruprecht, 1938,[9] and Root and associates, 1939.[10] The defect has not been abolished by insulin therapy and constitutes one of the chief disabling complications of diabetes today. There seem to be no essential differences between the blood vessel changes that occur in diabetes and those that develop in old age and are often attributed to senility. It is the purpose of this paper to record the occurrence of arteriosclerosis in depancreatized dogs in greater incidence than that commonly found in this species.

*This work has been aided by grants from the Josiah Macy, Jr., Foundation, the Committee on Research in Endocrinology of the National Research Council, the Eli Lilly Company, and the Douglas Smith Foundation for Medical Research of the University of Chicago.

†Presented in part at the meeting of the American Physiological Society in Toronto, April 26 to 29, 1939.

According to Fox,[11] the domestic dog rarely exhibits arteriosclerosis. After the fifth year hyperplasia of the intima may occur, but the deposition of calcium is very rare. In the wild relatives of the dog arteriosclerosis was found in 3 of 192 specimens of material in a zoo. The life span of these animals was one-third longer than the average for their family.

In 1924 Fisher[12] observed very marked arteriosclerosis of the aorta in a partially depancreatized dog that had survived the operation for eight months.

EXPERIMENTAL OBSERVATIONS

1. *The Incidence of Arteriosclerosis in Depancreatized Dogs.*—The material upon which this report is based consists of mongrel dogs of both sexes obtained from the city pound and subjected to partial or complete pancreatectomy. During the past five years, we have had under observation approximately 225 depancreatized animals in which the diabetes was fairly accurately controlled with both regular and protamine zinc insulin. For the most part these animals were used in the investigation which resulted in the demonstration of a second internal secretion of the pancreas, apart from insulin, and which has been designated lipocaic as having to do with the utilization of fat. Reports of this work have appeared elsewhere.[13]

During the course of routine autopsies in connection with this study, we have found varying degrees of arteriosclerosis of the aorta in 10 completely depancreatized and in 1 partially depancreatized animal. In the earlier part of the work sufficient attention was not paid to the possibility of alterations in the blood vessels and careful examinations of this region were not made. The 11 instances in which changes were found occurred in the last 80 animals coming to autopsy, which would indicate an incidence of about 13 per cent. The lesions have been observed most frequently as small raised pale yellow or white nodules in the intima of the thoracic and abdominal aorta, arranged in clusters about the orifices of the intercostal, mesenteric, and renal arteries and in the first part of the aorta near the base of the aortic valves (Figs. 1 and 2). Microscopically, all degrees of involvement have been found, from proliferation and thickening of the intima, deposition of amorphous lipoid material in the subintimal layers, and disruption of the media with deposition of amorphous lipoid and calcareous material (Figs. 3-7). These changes have been found commonly in dogs from five to nine months after pancreatectomy, but lesions of lesser extent have been observed as early as five weeks after the operation. The observation of typical atheromatous areas in the aorta of a depancreatized dog only six months old (Fig. 8) that was raised in the laboratory is especially interesting since it indicates that this complication can occur in very young animals. Abbreviated protocols of two of the animals follow.

PROTOCOLS

Dog 665.—Male, mongrel, aged about 1 year. Pancreatectomy on Aug. 24, 1937. Diet: bread, meat, and milk, containing approximately 25 per cent fat. Diabetes controlled with protamine insulin, 4 units daily. By Sept. 24, 1937, liver became very fatty (40 per cent fat). Lipocaic given from Nov. 11, 1937, to Feb. 26,

Fig. 1.—Dog 665. Photograph showing arteriosclerosis at the base of the aortic valves and about the orifices of the coronary arteries in a dog nine months after pancreatectomy.

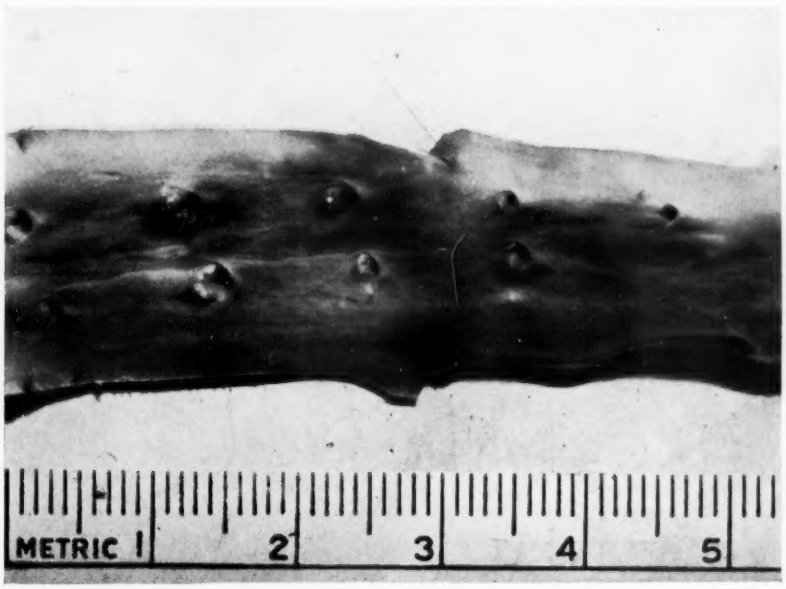

Fig. 2.—Dog 665. Photograph showing numerous raised yellow nodules in the intima of the thoracic and abdominal aorta at the orifices of the branching vessels in a dog nine months after pancreatectomy.

1938; clinical improvement and liver fat decreased to 8 per cent. Lipocaic stopped and animal became progressively weaker, lost weight, and died May 12, 1938.

Autopsy: Liver grossly normal; contained 6 per cent fat; no pancreas found; other organs, with exception of aorta, normal. When the aorta was opened, yellow-white nodules were seen and palpated on the intimal surface within the recesses of

Fig. 3.—Dog 665. Photomicrograph showing details of lesions seen in Fig. 1, thickening of the intima, deposition of amorphous lipoid and calcareous material in the subintimal layers and in the media, and disruption of the fibers in the media.

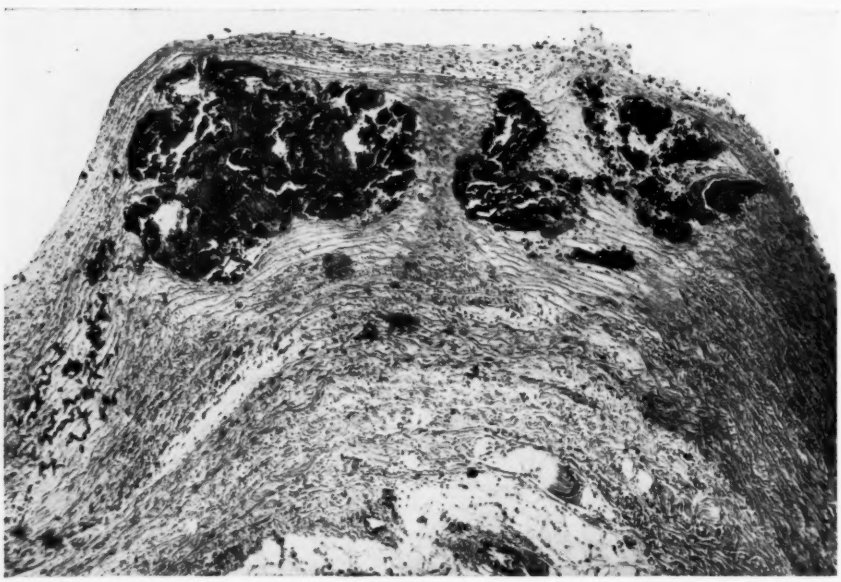

Fig. 4.—Dog 665. Photomicrograph showing details of lesions shown in Fig. 2. Note intimal thickening and deposition of calcium and amorphous lipoid material in the media and in the layers beneath the intima.

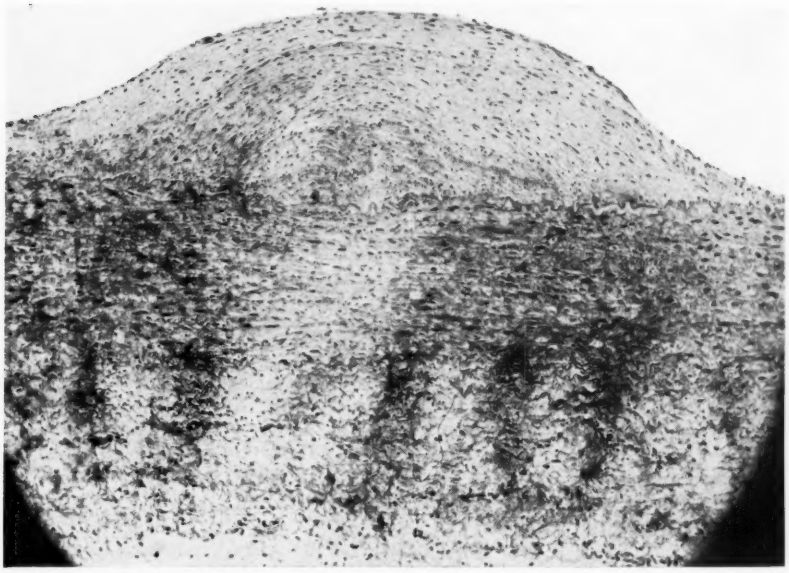

Fig. 5.—Dog 241. This animal died five months after pancreatectomy and at autopsy nodules were found in the intima of the thoracic and abdominal aorta, as shown in Fig. 2. This section illustrates proliferation of intimal cells of the connective tissue type without disruption of the internal elastic lamina.

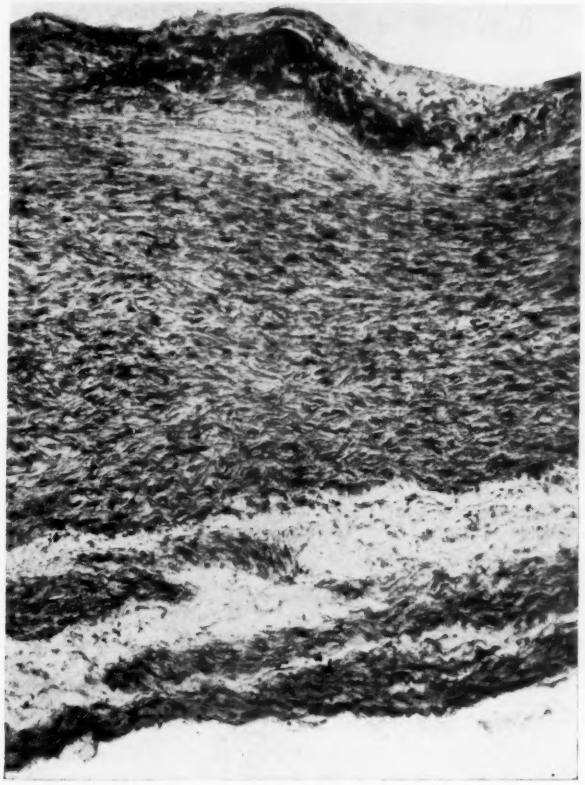

Fig. 6.—Dog 241. Photomicrograph showing thickening of the intima and deposition of calcareous and lipoid amorphous material beneath the intima in a dog five months after pancreatectomy.

the aortic valves (Fig. 1) and the aortic ring felt calcified. Similar yellowish white raised nodules were observed in the intima near the ostia of the branches of the thoracic and abdominal aorta (Fig. 2). In the abdominal aorta, near the ostia of the celiac and renal arteries, could be seen faint white or yellow longitudinal streaking of the intima for a distance of 3 to 5 cm. Microscopic examination of these lesions (Figs. 3 and 4) revealed a marked hyperplasia of the intima, disruption of the media, and deposition of amorphous calcium and lipoid material in the deeper intimal layers and in the media.

Fig. 7.—Dog 287. This animal died six months after pancreatectomy and at autopsy numerous small yellow nodules were found in the intima of the abdominal aorta and near the base of the aortic valves, as shown in Figs. 1 and 2. Section shows deposition of lipoid and calcareous material in the media.

Dog 241.—Female, mongrel, aged about 2 years, weight 7.8 kg. Pancreatectomy on March 18, 1937. Diet same as for Dog 665. Diabetes controlled with protamine insulin, 8 to 14 units daily. On June 15, 1937, the liver was found to contain 32 per cent fat and the daily administration of lipocaic was started. On July 30, 1937, the liver fat was normal and lipocaic was discontinued. The animal then gradually lost weight and strength and died probably from an insulin convulsion on Aug. 14, 1937. Autopsy revealed a moderate fatty infiltration of the liver. No pancreas was found. The first portion of the aorta was normal, but numerous small pale yellow nodules (1 to 2 mm. in diameter) were seen in the intima of the thoracic and abdominal aorta near the ostia of the aortic branches. Microscopic examination revealed marked proliferation of the intima (Fig. 5) and in some deposition of amorphous lipoid and calcareous material in the subintimal layers (Fig. 6).

2. *The Incidence of Arteriosclerosis in Normal or Nondiabetic Dogs.*—As indicated in the report by Fox referred to above, the occurrence of arteriosclerosis in normal domestic dogs has rarely been observed. However, during the past year we have examined the aortas of 75 normal or nondiabetic dogs, obtained from the same source, and somewhat to our surprise found definite arteriosclerosis lesions in 4, or about 5 per cent. These lesions were exceedingly small, consisting usually of one or two pale yellow or white nodules from 0.5 to 1 mm. in diameter and found usually in the first part of the aorta near the base of the aortic valves. Microscopic sections revealed essentially the same changes in the intima and media seen in the depancreatized animals.

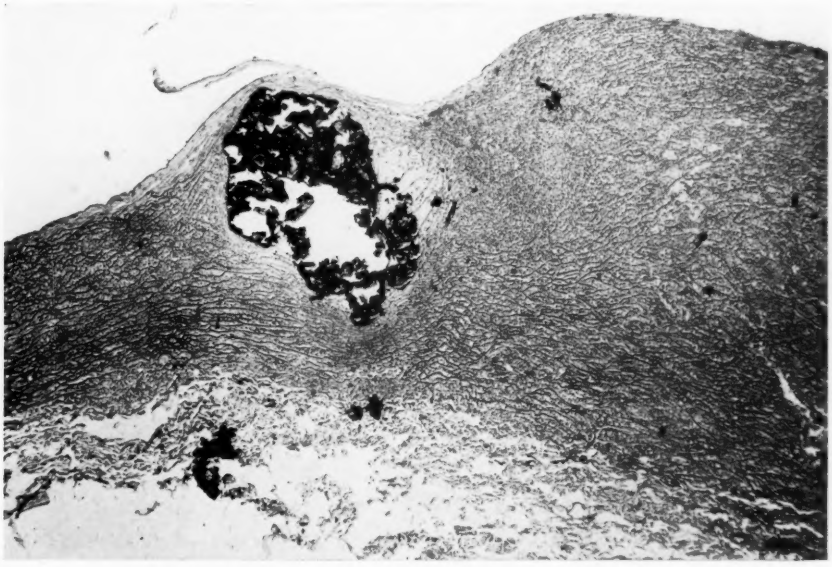

Fig. 8.—Dog D-27. Photomicrograph showing arteriosclerosis of the aorta in a dog seven weeks after pancreatectomy. This animal was reared in the laboratory and was only seven months old at the time of death. A very marked fatty infiltration of the liver occurred and death resulted from the biopsy.

DISCUSSION

The finding of a higher incidence and great severity of arteriosclerosis in depancreatized dogs than in normal animals of this species presents another point of resemblance between pancreatic diabetes and diabetes mellitus as it occurs spontaneously in man. It seems probable then that factors found to be operative in the one case may be of significance in the other and that both in turn may throw some light on the pathogenesis of nondiabetic arteriosclerosis. Considerable evidence has accumulated incriminating certain factors in the development of presenile arteriosclerosis in diabetes mellitus and it is interesting that here, too, certain resemblances may be seen between the disease in man and in the experimental animal. While there has been some dissent, a number of writers (Joslin,[5] Rabinowitch,[7] and others) have voiced their

conviction that the incidence of arteriosclerosis in diabetes mellitus is especially high when diets rich in fat are employed and that conversely it has become more rare with the adoption of a low fat, high carbohydrate regimen. This suggests that some residual defect remains in diabetes mellitus even with adequate insulin therapy. Several years ago one of us (L. R. D.)[14] raised the question: "Does this mean that many diabetics suffer from not only an insulin deficiency but also from a deficiency of lipocaic, which manifests itself in a disturbance in fat utilization, with the deposition of fat in the liver and in more chronic cases in the subendothelial layers of the arteries?"

There is some reason to believe that the atherosclerosis of the aorta in our depancreatized dogs may be due to lipocaic deficiency. Other investigators, with the exception of Fisher, have not observed this compliation. Practically without exception these have followed the practice of Macleod and his associates[15] of feeding fresh pancreas daily in addition to giving insulin. Fisher did not give fresh pancreas. The animals in our series that developed arteriosclerosis were maintained for varying periods of time on relatively insufficient amounts of lipocaic. For the most part they were used to assay the amounts of lipocaic in various pancreatic extracts and in this connection were allowed to develop the fatty livers of lipocaic deficiency alternating with periods of control.

Chaikoff and Kaplan,[16] however, were able to keep depancreatized dogs alive for from one to five years by means of insulin but without providing raw pancreas or supplementary choline or betaine in the diet. These animals were not found to have arteriosclerosis. Examination of their paper reveals the interesting fact that these animals were provided a diet, adequate from the nutritive standpoint, but containing very small amounts of fat; i.e., only that present in raw lean beef. In a recent paper we[13b] have reported the striking fact that the depancreatized dog on a low fat diet may survive for long periods on insulin alone; whereas, a high fat diet promptly produces the symptoms of lipocaic deficiency. In the series of animals reported here that developed arteriosclerosis, all were supplied diets containing from 25 to 45 per cent fat and active pancreatice juice was occasionally supplied to improve digestion and absorption.

SUMMARY

Arteriosclerosis of the aorta has been observed in 10 completely and 1 partially depancreatized dogs in our laboratory, representing an incidence of about 13 per cent where this complication was looked for. Lesions similar in nature but much less extensive were observed in 4 of 75 normal dogs of the same type and size and obtained from the same source, or an incidence of about 5 per cent. The depancreatized animals were well controlled with insulin and maintained on relatively high fat diets. Without exception these animals were given insufficient amounts

of lipocaic to maintain normal fat metabolism as evidenced in some cases by repeated accumulations of fat in the liver and other findings indicative of lipocaic deficiency. The possible role of lipocaic deficiency in the presenile arteriosclerosis of diabetes mellitus and pancreatic diabetes is discussed.

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THE ANATOMIC AND PHYSIOLOGIC EFFECTS OF AN ARTERIOVENOUS FISTULA*

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SIGNIFICANCE OF DIMINUTION IN CARDIAC SIZE ON OPENING A FISTULA

THAT an arteriovenous fistula has profound effects upon the circulatory system is universally recognized, although the explanation for some of these effects is still subject to controversy. Particularly puzzling has been the effect upon the size of the heart, which is said invariably to become enlarged in consequence of the fistula. This enlargement has been attributed by some solely to dilatation,[1] but by others to a high degree of hypertrophy.[2] A startling fact, however, is the observation, repeatedly made, that in the first twenty-four hours after the establishment of an experimental arteriovenous fistula, the heart diminishes in size, followed in succeeding days by a gradual enlargement of the heart. Inasmuch as this sequence of events has recently been questioned,[3] the following observations are presented:

ANIMAL 8.—(Fig. 1.) Female adult dog; weight, 9 kg. An aorta-vena cava fistula was established on Jan. 24, 1939; aorta, 6.5 mm. in diameter; vena cava, 8.5 mm. in diameter; fistula, 5.5 mm. long. Before opening the fistula (10:45 A.M.), a roentgenogram of the chest was taken (pulse, 120). At 11:15 A.M. a second roentgenogram showed a slight diminution in cardiac size (pulse, 120). At 1:30 P.M. the cardiac size was even smaller (pulse, 132), and at 4:00 P.M. the heart was remarkably smaller (pulse, 200). At this time there was marked edema of both lower extremities. The animal died at 6:00 o'clock, two hours later.

ANIMAL 4.—(Fig. 2.) Adult male; weight, 12 kg. An aorta-vena cava fistula was established on Dec. 21, 1938; aorta, 7 mm. in diameter; vena cava, 10 mm. in diameter; fistula, 7 mm. long. Before opening the fistula a roentgenogram of the chest was made (pulse, 88). All clamps (proximal artery, distal artery, distal vein) were removed except the clamp on the vein proximal to the fistula. No bruit or thrill developed and the pulse increased only to 104. After releasing the clamp on the proximal vein, a loud bruit was heard immediately and an intense thrill could be felt. The pulse now increased to 140. A roentgenogram four hours after operation showed a remarkably small heart (pulse, 160). The next morning the animal was found dead.

ANIMAL 7.—Male pup; weight, 6.8 kg. An aorta-vena cava fistula was established Jan. 10, 1939; aorta, 5.5 mm. in diameter; vena cava, 8 mm.; fistula, 4 mm. long. Before opening the fistula a roentgenogram of the chest was made (pulse, 120). One hour after opening the fistula, a definite decrease in the size of the heart was noted (pulse, 132). Two days later there was still a slight reduction in the size of the heart. On Jan. 17 a definite increase in the cardiac shadow had occurred (pulse,

*This study was aided by a grant from the Fluid Research Fund of the Rockefeller Foundation.

170). There was no edema, but the abdominal veins were very prominent and a loud continuous bruit could be heard over the lower abdomen. The posterior extremities were very weak. On Feb. 16 the animal was killed in a fight.

ANIMAL 5.—(Fig. 3.) An adult female collie; weight, 13 kg. An aorta-vena cava fistula was established on Dec. 17, 1938; aorta, 7 mm. in diameter; vena cava, 9 mm. in diameter; fistula, 5.5 mm. long. A roentgenogram was taken before opening the fistula (pulse, 132). Five hours after opening the fistula a marked diminution in cardiac size had occurred (pulse, 160). On Jan. 3, a slight cardiac dilatation

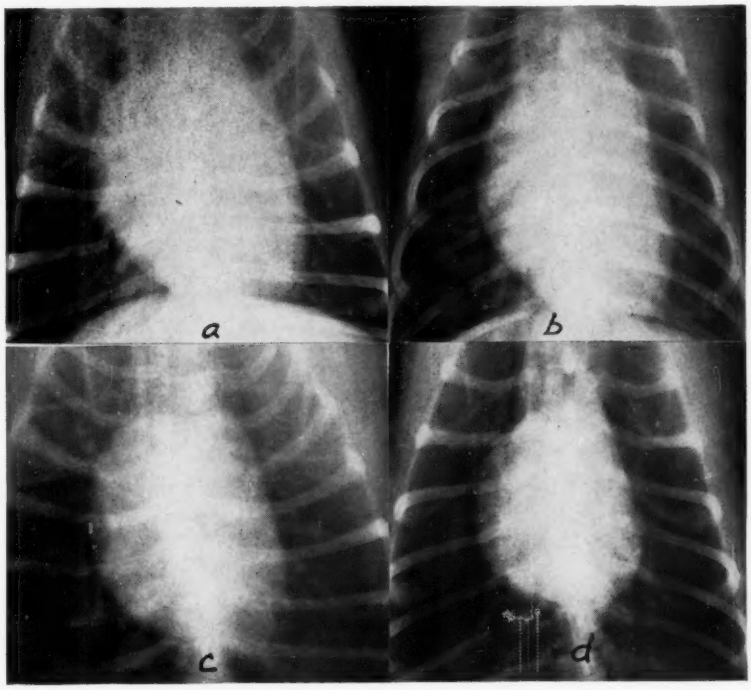


Fig. 1.—Animal 8. Roentgenograms of heart following establishment of an aorta-vena cava fistula. *a*, 10:45 A.M., just before opening fistula; *b*, 11:15 A.M., fifteen minutes after opening fistula; *c*, 1:30 P.M.; *d*, 4:00 P.M. At 6 P.M. the animal died as the result of the fistula.

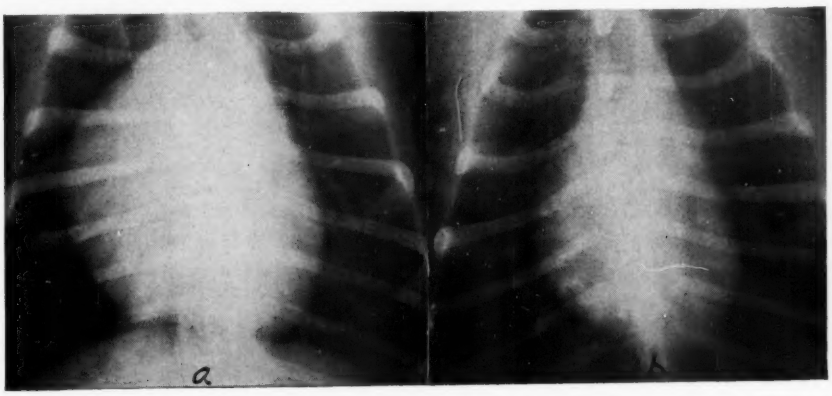


Fig. 2.—Animal 4. Roentgenograms illustrating reduction in size of heart four hours after opening an aorta-vena cava fistula. The animal died a few hours later. *a*, Normal heart; *b*, four hours after operation.

was noted (pulse, 180), and on Feb. 21 a marked dilatation was present (pulse, 156). At this time it was also noted that the abdominal wound was discharging pus, and, although a loud bruit was then present, from this time forward the bruit gradually diminished and finally disappeared entirely. Necropsy (Aug. 17, 1939) showed closure of fistula by thrombosis and fibrous contraction.

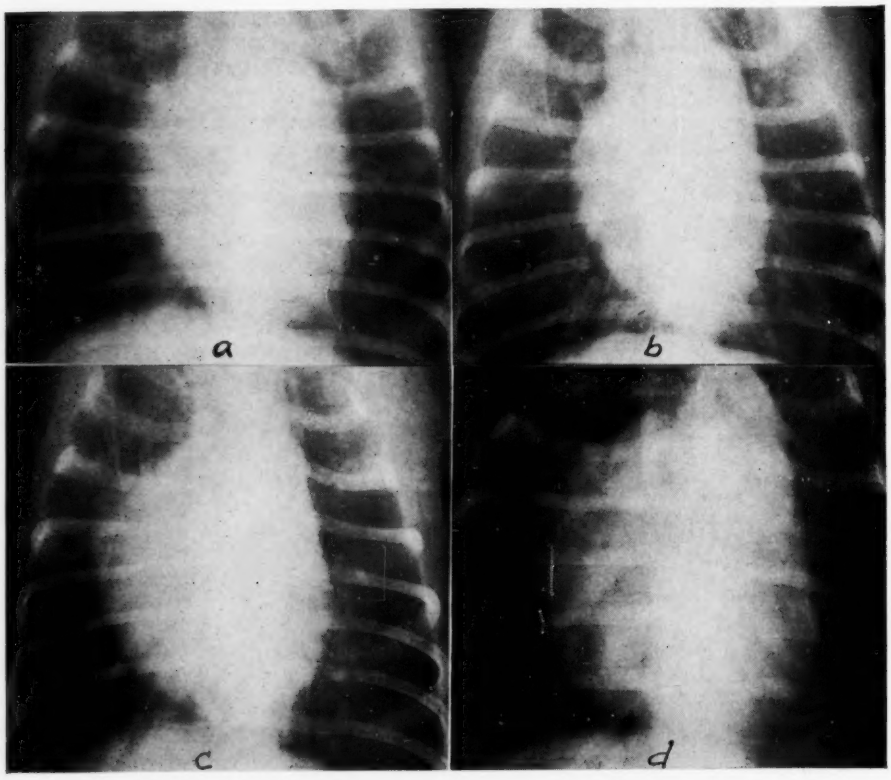


Fig. 3.—Animal 5. Roentgenograms illustrating diminution in cardiac shadow within four hours after establishing an aorta-vena cava fistula, a definite, though slight, dilatation five days later, and a marked dilatation seven weeks later.

ANIMAL 3.—Adult male; weight, 15 kg. On June 30, 1938, a fistula between the right femoral vessels was established: artery, 4.5 mm. in diameter; vein, 6 mm. in diameter; fistula, 2.4 cm. long. A roentgenogram was made before opening the fistula (pulse, 104). Immediately after opening the fistula the pulse rate increased to 130. At the same operation, a fistula between the left femoral vessels was established: artery, 4.5 mm. in diameter; vein, 6 mm. in diameter; fistula, 2.7 cm. long. Before opening this second fistula the pulse rate was 144. After opening the second fistula the pulse rate rose to 160. Six hours later a roentgenogram showed a definite diminution in cardiac size. Both lower extremities were considerably swollen and edematous. Within six days this edema subsided, but the superficial veins became quite prominent. Within five days the heart recovered its normal size (pulse, 160), and a month later it was considerably larger than normal (pulse, 156). The animal is still living.

These variations in cardiac size incident to an arteriovenous fistula are directly comparable with the reduction in the size of the heart accompanying shock. In an acute experiment, under nembutal anes-

thesia, an adult dog was given 0.5 c.c. of histamine (1:1,000) causing a marked fall in blood pressure from 144 mm. to 66 mm. Hg (Figs. 4, *1* and *2*). Coincident with this fall in blood pressure there occurred a marked reduction in cardiac size (Figs. 4, 1^1 and 2^1). Histamine shock is produced by peripheral vasodilatation. This results in a redistribution of the circulating blood volume, decreasing it in the central circulatory bed and increasing it in the peripheral bed. As a direct consequence of this redistribution of blood volume, the heart is reduced in size. In the same experiment the animal was permitted to recover both its blood pressure and its normal cardiac size (Fig. 4). Again,

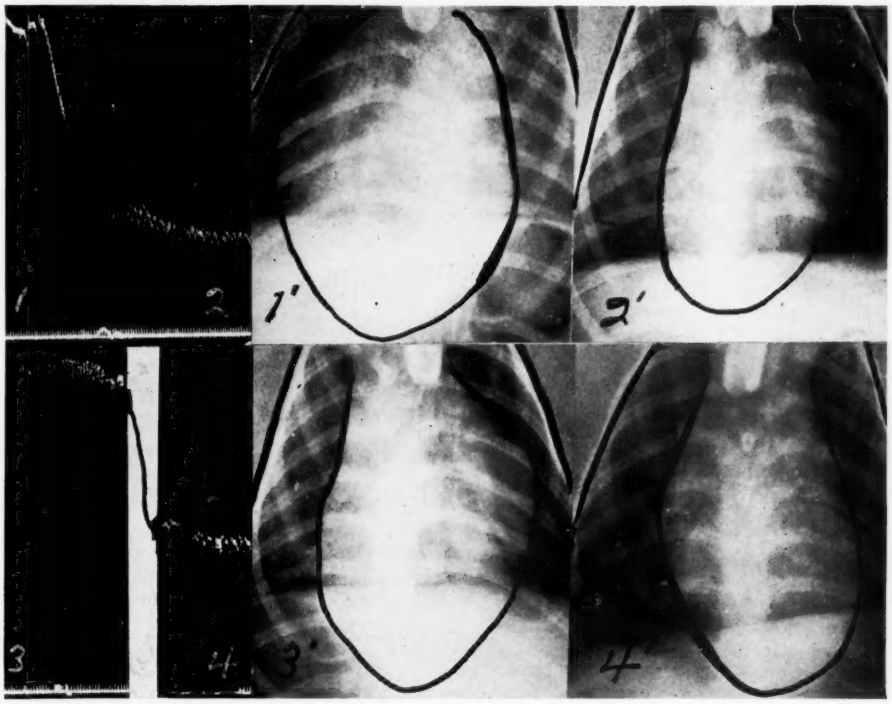


Fig. 4.—Shock and cardiac size. The kymographic record (*1* and *2*) illustrates the fall in blood pressure produced by an injection of 0.5 c.c. histamine. Coincident with this histamine shock the heart decreased in size as shown in roentgenograms 1^1 and 2^1. Following recovery of blood pressure (*3*) and cardiac size (3^1), shock (*4*) was produced again by trauma upon the thigh, accompanied again by a decrease in cardiac size (4^1).

shock was precipitated by heavy and repeated blows on one thigh. The mechanism underlying this shock is undoubtedly related to the loss of blood into the traumatized area.[4, 5] The development of shock and drop in blood pressure (Fig. 4, *3*) was accompanied by a corresponding reduction in cardiac size (Fig. 4, 3^1). Again this is explicable on a redistribution of the total blood volume, the blood lost into the peripheral tissues being abstracted from the central circulatory bed.

Exactly comparable observations have been made incident to severe blood letting. A progressive diminution in cardiac size accom-

panied massive external hemorrhage (Fig. 5), followed by recovery of the heart to normal size as the withdrawn blood was restored to the circulatory system.

The opening of an arteriovenous fistula also causes bleeding, but in these circumstances the bleeding does not occur to the outside nor into the tissues, but into a capacious venous system distal and proximal to the fistula, capable of storing in it a large volume of blood. This redistribution of blood from the central circulatory bed into the peripheral venous bed is accompanied inevitably by a reduction in the size of the heart, provided the fistula permits a sufficient diversion

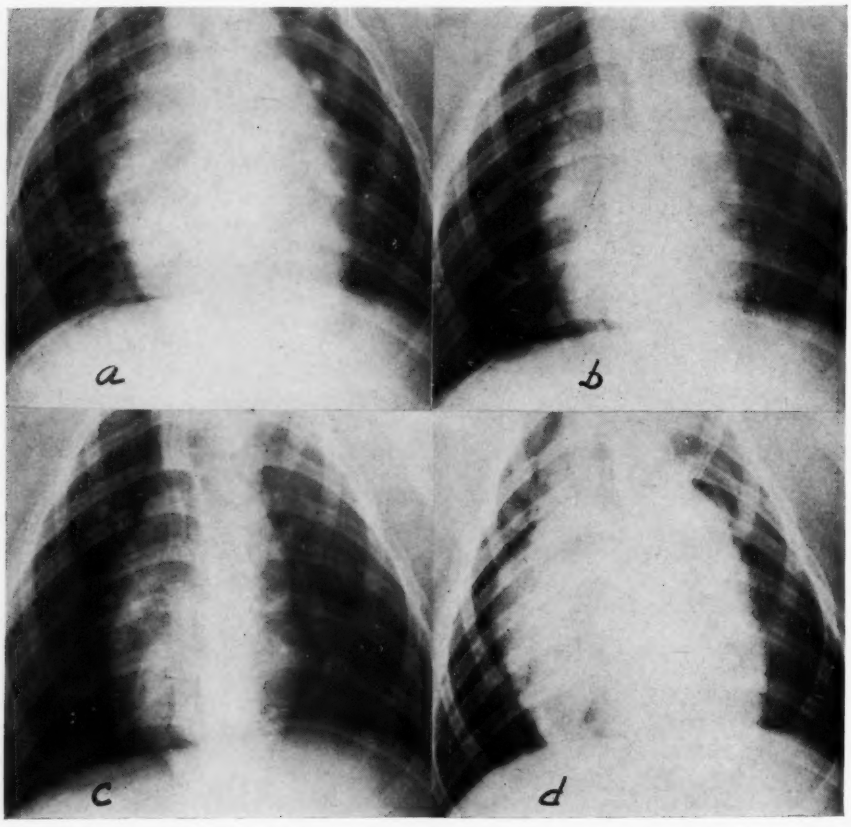


Fig. 5.—Roentgenograms illustrating the direct relationship between size of heart and total volume of circulating blood. *a*, Normal heart of 12 kg. dog; *b*, after removal of 200 c.c. blood from femoral artery; *c*, after removal of additional 300 c.c. blood; *d*, after restoration of 400 c.c. blood into femoral vein. The size of heart is even larger than the normal heart due to accretion of fluid from tissues into the circulatory bed during the bleeding process.

of blood from the arterial bed. The diminution of the cardiac size in these instances was quite independent of the rate of cardiac contraction, since subsequent dilatation was often accompanied by a pulse rate equal to or higher than the rate when the heart was diminished in size.

Such effects upon the heart are dependent upon two conditions; namely, the size of the fistula and its location in the arterial tree. In

establishing an aorta-vena cava fistula, the animal invariably died if the lateral anastomosis produced between the two vessels equaled in length the diameter of the aorta. In such instances, the diversion of blood into the venous bed was excessive, the blood pressure in the cerebral, coronary, and renal arteries was reduced to a minimum, the heart diminished markedly in size, and death followed.

In establishing a femoral fistula, the lateral anastomosis between the vessels can be 2 and 3 cm. in length, since the volume of blood diverted into the venous bed is limited by the diameter of the proximal artery. As the proximal artery dilates, the long lateral anastomosis permits an increasing leakage of blood into the venous bed, and the usual physiologic and anatomic effects invariably will occur. Experience has taught us that, unless the small femoral vessels are joined through long lateral anastomoses, the opening will close by thrombosis and cicatricial contraction. Small openings cause so little diversion of blood that no measurable physiologic or anatomic changes will occur; i.e., measurable by present instruments of precision. End-to-end anastomoses have usually proved to be quite ineffective in producing these physiologic results, since complete division of the artery is followed by an elastic contraction both in length and in transverse diameter of the vessel, so that the fistula is, and remains, too small for an effective diversion of blood.

When fistulas compatible with life but still capable of diverting a large volume of blood are established, the reduction in size of the heart is invariably followed by a gradual dilatation of the heart, in some instances of remarkable degree, as the following experiments demonstrated.

INCREASED CAPACITY OF CIRCULATORY SYSTEM DUE TO CARDIAC DILATATION AND DILATATION OF ARTERY AND VEIN BETWEEN THE FISTULA AND HEART, WITH A CONCOMITANT INCREASE IN TOTAL BLOOD VOLUME

To determine more exactly the effects of an arteriovenous fistula, the following experiments were undertaken in the growing animal. Three puppies from the same litter, born July 6, 1938, all approximately equal in size and weight, were chosen for the experiment, one being kept as a control.

PUP 1.—Male; weight, 9 kg. On Nov. 29, 1938, an aorta-vena cava fistula was established: aorta, 6 mm. in diameter; vena cava, 8 mm. in diameter; fistula, 5 mm. long. The pulse rate was immediately accelerated from 120 to 172 on opening the fistula. According to roentgenograms, a slight diminution in the cardiac shadow occurred immediately after the opening of the fistula, but within twenty-four hours the heart had recovered its original size, followed in the succeeding months by a truly enormous enlargement of the heart. At all times after the establishment of the fistula, good femoral pulsations were present on both sides. On April 24, 1939, the pulse rate was 192; respirations, 52; the heart was very much enlarged and there was great dyspnea on exertion. On Nov. 7, 1939, the animal was in much better condition; there were no edema and no ascites;

good femoral pulsations were palpable, large veins (Fig. 11) were visible over the abdominal wall, and a loud bruit was audible over the lower abdomen. On this date, approximately one year after the establishment of the fistula, the carotid artery was cannulized to obtain a continuous record of the blood pressure. The fistula was exposed and closed by compression. Immediately there occurred a pronounced increase in blood pressure and a fall in pulse rate (Fig. 6). Analyzing this kymographic record, we find that closure of the fistula increased the mean systolic pressure from 186 to 236 mm. Hg immediately after closing the fistula, dropping to a level of 212 mm. Hg as long as the fistula remained closed, falling precipitately on opening the fistula to 140 mm. Hg, but recovering promptly within a few beats to the previous level of 186 mm. Hg. Variations in pulse rate paralleled these changes in blood pressure. The animal was killed, and examination revealed an aorta dilated from the heart to the fistula and a greatly dilated vena cava from the fistula to the heart. The heart almost filled the chest. The fistula admitted a bougie having a circumference of 18 mm. The circulatory system was injected with bismuth oxychloride in gum acacia (Fig. 8). The heart weighed 176 gm.; weight of animal, 11.1 kg. (Fig. 9).

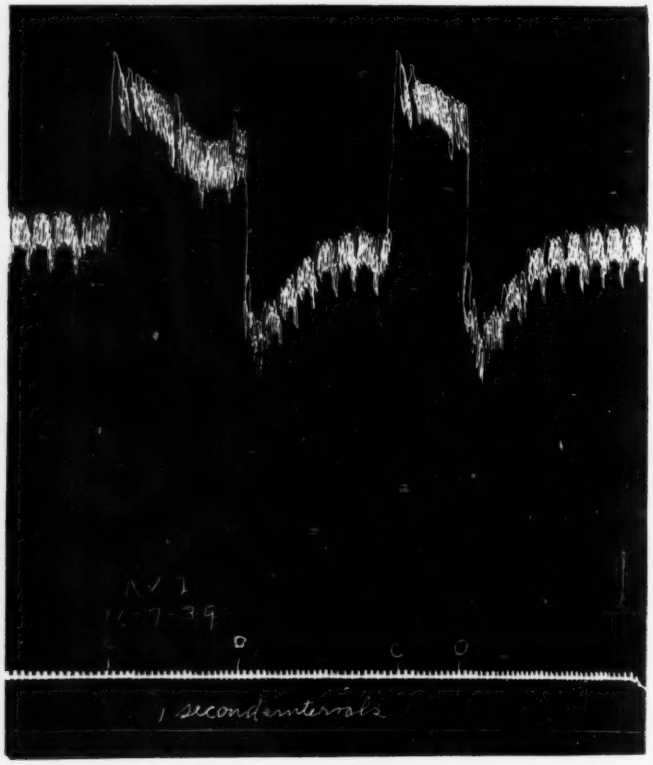


Fig. 6.—Pup 1. Marked elevation of blood pressure and reduction in pulse rate on closing an aorta-vena cava fistula of eleven months' duration.

Pup 3.—Male; weight, 8.3 kg. On Dec. 6, 1938, an aorta-vena cava fistula was established: aorta, 5 mm. in diameter; vena cava, 8 mm. in diameter. On opening the fistula the pulse rate rose from 132 to 160. On the following day a good pulse could be palpated in both femoral arteries, there was no edema, and the pulse rate was 180. A roentgenogram taken twenty-four hours after establishing the fistula showed a definite decrease in the size of the heart. On Dec. 8, 1938, the heart had

Fig. 7.—The dilatation of the heart is commensurate with the size of the fistula: *a*, Heart of control dog; *b*, heart of Pup 1 with an aorta-vena cava fistula 18 mm. in circumference; *c*, heart of Pup 2 with an aorta-vena cava fistula 12 mm. in circumference. All animals from the same litter and of equal size and weight.

recovered its previous size; there was a good femoral pulse to be felt in both groins, and the pulse rate was 200. The animal continued in good health until Oct. 27, 1939. On this date, the heart had increased greatly in size, although not as much as the heart of the litter mate (Figs. 7 and 9). The pulse rate was 140. A good femoral pulse could be felt on both sides, and there was no edema. The fistula was exposed and compressed, causing a fall in pulse rate from 140 to 104.

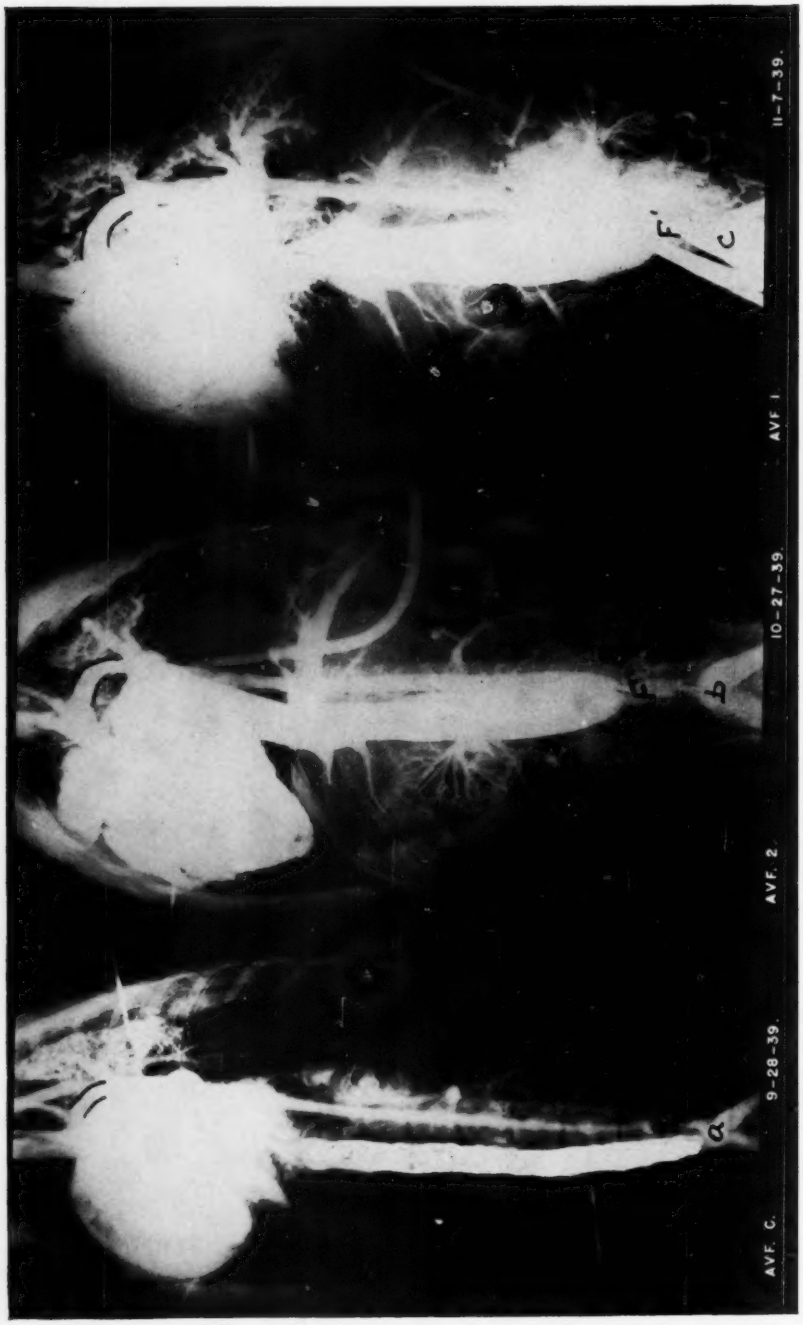


Fig. 8.—Roentgenograms of three litter mates following injection of circulatory system with bismuth oxychloride. *a*, Normal heart, aorta, and vena cava of control animal; *b*, moderate dilatation of heart, aorta, and vena cava following establishment of aorta-vena cava fistula at *F*, which at death proved to be 12 mm. in circumference; *c*, great dilatation of heart, aorta, and vena cava incident to fistula at F^1, 18 mm. in circumference. These injections prove that the dilatation involves the entire circulatory system through which the short-circuited blood passes; namely, the aorta from heart to fistula, the vena cava from fistula to heart, and all chambers of the heart.

The animal was killed and the circulatory system injected with bismuth oxychloride in gum acacia. The aorta and vena cava were both dilated from the fistula to the heart (Fig. 8) and the heart was greatly enlarged. The heart weighed 123 gm.; weight of animal, 10 kg. (Fig. 9). From the lesser cardiac enlargement as compared with Pup 1, it was considered probable that the fistula was smaller in this animal than in Pup 1. This proved to be the case. The fistula admitted a bougie having a circumference of 12 mm., as compared with 18 mm. in Pup 1.

The control animal was also killed on this date, and the heart and circulatory system injected with bismuth oxychloride (Fig. 8). The heart weighed 74 Gm.; weight of the animal, 11.6 kg. (Fig. 9).

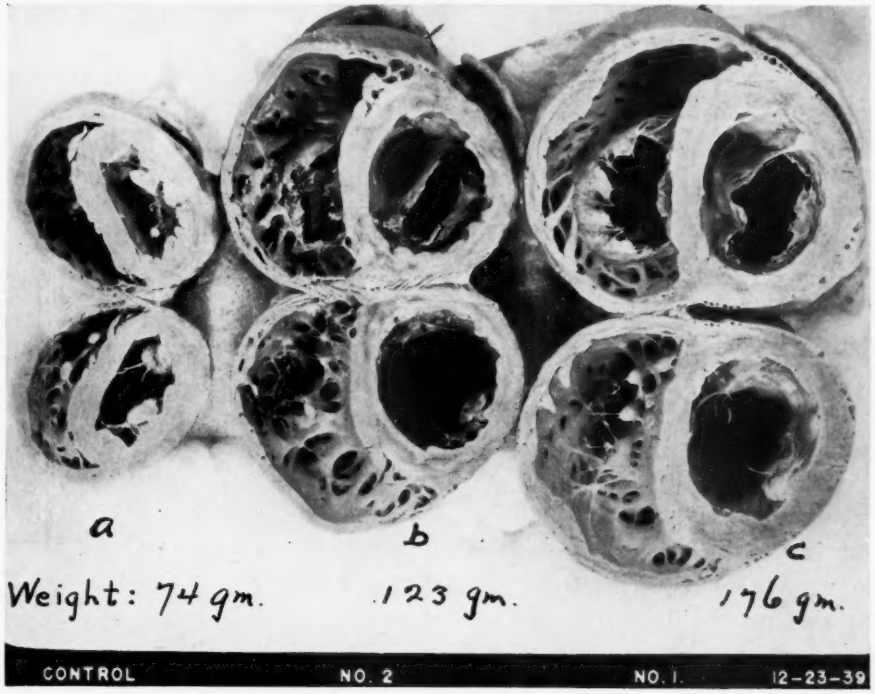


Fig. 9.—Cross-section of hearts of three litter mates: *a*, Control animal; *b*, pup with aorta-vena cava fistula 12 mm. in circumference; *c*, pup with aorta-vena cava fistula 18 mm. in circumference. The cardiac dilatation and hypertrophy were commensurate with the size of the fistulas.

The extraordinary dilatation and hypertrophy of the heart consecutive to these fistulas in the growing animal contrast somewhat with previous observations in adult animals. In the latter instances the enlargement seemed to be mainly a dilatation, although hypertrophy also occurred to a minor degree. In Pup 1 three months after establishing the aorta-vena cava fistula, evidences of relative cardiac insufficiency were present, such as great dyspnea in the presence of a greatly enlarged heart. The enlargement up to this time was probably mainly due to dilatation. Six months later the animal was much less dyspneic and was in better general condition. The heart, however, was even larger than before, and at necropsy an astonishing hypertrophy was present (Fig. 9). The probable explanation is that

in the intervening months hypertrophy had "caught up" with the previous dilatation. It is suggested that, when dilatation outstrips hypertrophy, relative decompensation occurs; when hypertrophy parallels dilatation, enormous enlargement may occur without decompensation.

Various authors,[6, 7] following the lead of Lewis and Drury, have ascribed the enlargement that occurs in an arteriovenous fistula mainly to a dilatation consecutive to a "deficient nutrition of the heart muscle consequent on the fall of mean arterial pressure." It is obvious that the degree of cardiac hypertrophy demonstrated in these growing animals is not compatible with a deficient nutrition of the cardiac muscle. Since it has been conclusively demonstrated that the dilatation involves the entire part of the circulatory system through which the short-circuited blood passes, including all chambers of the heart, and the artery and vein between the fistula and the heart, it can be dogmatically stated that the cardiac enlargement and the dilatation of the vessels are both due to the same cause; namely, to an increased bulk or volume of blood flowing through the shorter circuit. As Porter[8] ably states: "The enlargement of the artery and vein in the fistulous circuit and the increase in cardiac size are primarily an adjustment dilatation. There is a great increase in cardiac filling due to acceleration of the velocity of blood flow, and increase of effective venous pressure in the involved vein."

It has been repeatedly demonstrated that cardiac output is greatly increased and even doubled in the presence of a moderately sized fistula,[9] and numerous observations indicate that there is an increase in venous pressure in that part of the venous bed lying between a fistula and the heart. Although contrary to the conclusions of Lewis and Drury, these are established facts. It has never been contended that there is a "marked rise in general venous pressure," but that there is a rise in venous pressure proximal to a fistula, the extent of which depends upon the size and duration of the fistula, cannot be questioned.[8] When a fistula is opened, the increased velocity of flow through the vena cava may greatly increase the volume of blood delivered to the heart, and an efficient, undecompensated heart can effectively propel forward a greatly increased volume of blood delivered to it without a rise in general venous pressure, or even without much rise in lateral vena caval pressures. Porter concludes that "with adjustment dilatation of the artery and vein, the rate of the blood flow and the pressure in the vein decrease while the cross-section of the column of the returning circuit increases." It is apparent that the thin-walled, easily distensible vena cava lying free in a large cavity is capable of great adjustment dilatation, and a great increase in effective venous pressure at the portal of the heart may occur without necessarily increasing the general venous pressure.

Concomitant with the increase in the volume or bulk of blood flowing through the shorter circuit, attracted and diverted into it by reason of the decreased peripheral resistance in this circuit, another important compensatory phenomenon comes into play. In the immediate period following the opening of the fistula, the diversion of blood into the fistulous circuit abstracts blood from the general circulation with a marked concomitant fall in blood pressure. To compensate for this diversion and to restore a normal blood pressure to the general circulation, an increase in total blood volume occurs, which is large or small, depending upon the size of the fistula.[10]

The following observations on total blood volume in these three litter mates were made:

ANIMAL	DATES	WEIGHT	BLOOD VOLUME
Control	2/23/39	10.4 kg.	950 c.c.
	8/23/39	11.6 kg.	960 c.c.
Pup 2	2/28/39	10.5 kg.	1,190 c.c.
	9/20/39	10.7 kg.	1,210 c.c.
Pup 1	2/23/39	10.0 kg.	1,430 c.c.
	8/23/39	11.1 kg.	1,550 c.c.

By mathematical computation from measurements obtained in the roentgenograms of the injected animals (Figs. 8 and 10), the following approximate capacities were determined for that part of the circulatory system included in the shorter fistulous circuit, including the heart, the aorta from heart to fistula, and the vena cava from fistula to the heart:

	CAPACITY	TOTAL BLOOD VOLUME	INCREASE IN CAPACITY AS COMPARED TO CONTROL	INCREASE IN TOTAL BLOOD VOLUME AS COMPARED TO CONTROL
Control	200 c.c.	960 c.c.		
Pup 2	480 c.c.	1,210 c.c.	280 c.c.	250 c.c.
Pup 1	775 c.c.	1,550 c.c.	575 c.c.	590 c.c.

In these three litter mates, equal in weight and stature (Fig. 10), there was a surprising correlation between the increase in capacity of the shorter circuit and the increase in the total blood volume, both being commensurate with the size of the fistula. It may be inferred that, if no demonstrable dilatation of the heart or of the vessels proximal to the fistula occurs, there is probably also no demonstrable increase in blood volume. I believe that even small fistulas are accompanied by a minor dilatation of the heart and vessels and by commensurate increases in total blood volume, but our methods are not exact enough and our eyes not keen enough to demonstrate and to recognize such minor dilatations and such small increases in blood volume. It is freely granted that the dye method is not a very ac-

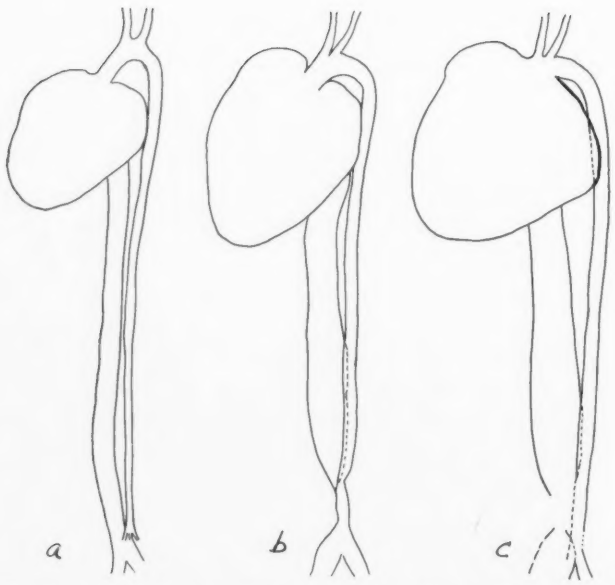


Fig. 10.—Tracings of injected specimens (Fig. 12) to illustrate dilatation and, therefore, increased capacity of that part of the circulatory system through which the blood short circuited by the aorta-vena cava fistula flowed. By mathematical computation the capacity of this part of the circulatory system was as follows: *a*, Control, 200 c.c.; *b*, Pup 2, 480 c.c.; *c*, Pup 1, 775 c.c.

Fig. 11.—Photograph of three litter mates, Dogs 1 and 2 having aorta-vena cava fistulas. *Dog 1:* Weight, 11.1 kg.; blood volume, 1,430 c.c. *Dog 2:* Weight, 10 kg.; blood volume, 1,210 c.c. *Control:* Weight, 11.6 kg.; blood volume, 960 c.c.

curate method of studying blood volume, but one cannot ignore these results obtained in animals of the same litter on successive occasions, nor can one escape the fact that if there is a considerable increase in the capacity of the circulatory system by dilatation, there must be an increase in blood volume to fill it.

THE EFFECTS OF BILATERAL FEMORAL FISTULAS

On Arterial Pressures.—In an animal in which bilateral femoral fistulas had been established on Oct. 31, 1934, the following observations (Fig. 12) were made on June 28, 1938. Under nembutal anesthesia

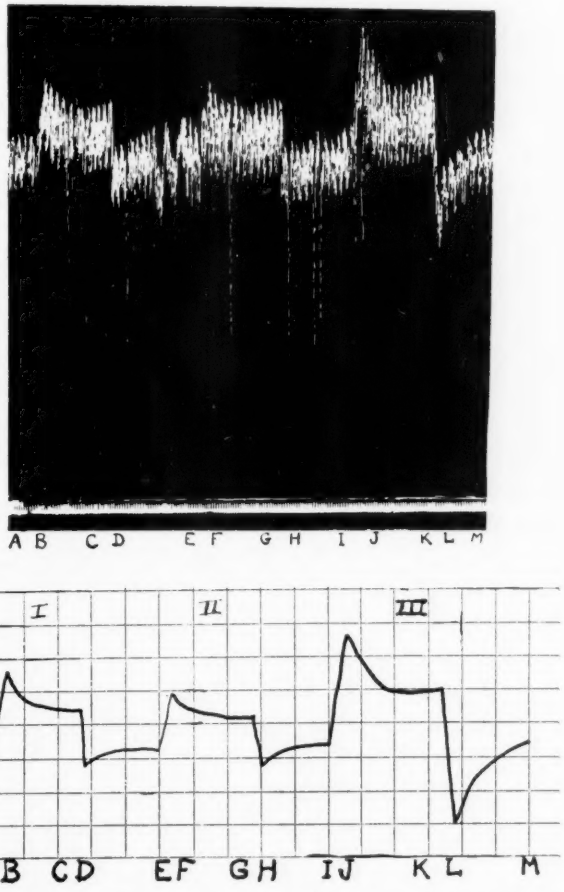


Fig. 12.—Kymographic record of carotid blood pressure in the presence of bilateral femoral fistulas. *A*, Both fistulas open; pulse, 102; *B*, *C*, right fistula closed; pulse, 87; *D*, *E*, both fistulas open; pulse, 98; *F*, *G*, left fistula closed; pulse, 82; *H*, *I*, both fistulas open; *J*, *K*, both fistulas closed simultaneously; pulse, 76; *L*, *M*, both fistulas opened simultaneously. The effects upon blood pressure and pulse depend upon amount of blood diverted into the venous bed.

and with aseptic precautions, the right carotid artery was cannulized and both fistulas in the groin were exposed to permit complete closure of the artery proximal to the fistula. On closing the right fistula, the blood pressure rose immediately from 124 (pulse, 102) to 146 mm. Hg, dropping to a level of 136 mm. Hg (pulse, 87) as long as the fistula

remained closed. On opening the fistula, the blood pressure dropped precipitately to 118 mm. Hg, rising promptly to a level of 122 mm. Hg as long as the fistula remained open. Similar figures were obtained on closing the left fistula (Fig. 12). On closing both fistulas simultaneously, the pressure rose precipitately to a high point of 156 mm. Hg (pulse, 76), dropping to a level of 140 mm. Hg as long as the fistula remained closed. On opening the two fistulas simultaneously, the pressure dropped to a low point of 100 mm. Hg for several beats only, rising promptly to the previous level of 124 mm. Hg.

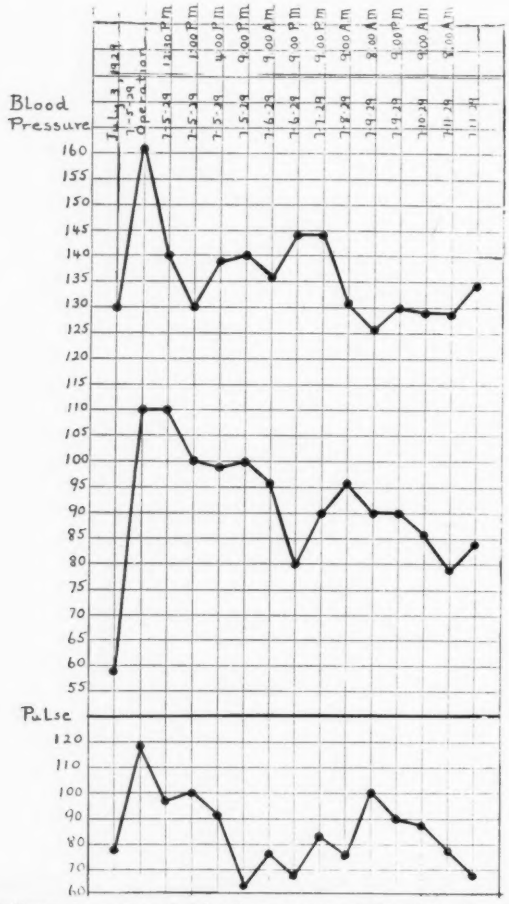


Fig. 13.—Variations in general blood pressure following the removal of a large carotid-jugular fistula of eighteen months' duration. For forty-eight hours, both systolic and diastolic pressures were excessively elevated due to overdistention of circulatory system by the increased blood volume that occurred in the presence of the fistula. Following operation, the total blood volume decreased from 8,900 to 7,800 c.c.

It was a convincing demonstration of the fact that the physiologic effects of opening and closing a peripheral fistula depend upon the volume of blood escaping into the shorter circuit.

The form of the blood pressure curve obtained on closing a fistula of long duration is unique and distinctly characteristic. Closing the fistula forces into the arterial bed the blood formerly leaking into the capacious venous system. The normal arterial tree, including the arch

of the aorta, becomes overdistended by the volume of blood by which the normal volume has been augmented since the introduction of the fistula. This overdistention causes a sudden and excessive, though temporary, increase in blood pressure, which is promptly rectified, so far as it is possible, by a general vasodilatation and, through the vagus, by a reduction in the rate of cardiac contractions. As a result, after two to three beats the blood pressure drops to a lower level, though it is still higher than when the fistula is open. A part of the increase in blood pressure is due, of course, to raising the peripheral resistance, but were it due solely to the elimination of an area of lessened resistance there would be a flat curve without the few initial beats of very high pressure. Indeed, the flat type of curve is obtained when a fistula is first established, before the blood volume has increased: Opening the fistula drops the blood pressure to lower diastolic and systolic levels; closing the fistula restores blood pressure to the previous levels, these changes being entirely due to reducing and increasing peripheral resistance.

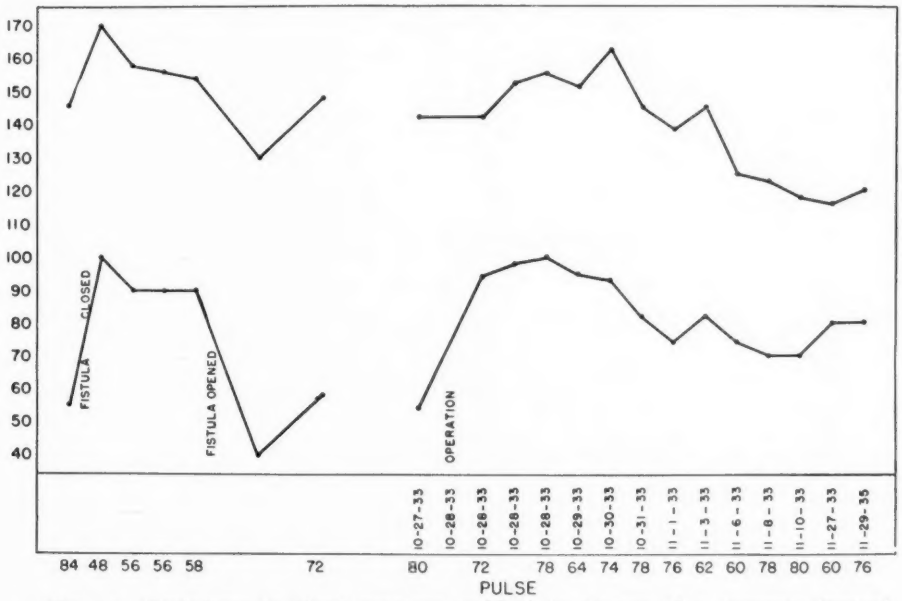


Fig. 14.—Variations in blood pressure incident to closure of a common femoral fistula of four years' duration. (a) By digital pressure; (b) by operative elimination. The blood volume decreased from 7,200 to 6,200 c.c. following operative removal of the fistula.

When a large fistula of long duration is permanently eliminated, the blood pressure curve also takes on a very characteristic form (Figs. 13-15). There is again a temporary increase both in diastolic and systolic pressures which then gradually subside to lower levels, the diastolic remaining permanently elevated, the systolic approximately the same as before the closure of the fistula. These transient increases can be explained only on one basis: the overdistention of the normal arterial bed by an abnormally large volume of blood which

requires several days for reduction and readjustment to the new conditions incident to the elimination of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased resistance.

The concept of an increase in total blood volume provides a logical and acceptable solution for the variations in blood pressure and pulse that characterize the opening and closing of the peripheral arteriovenous fistula.

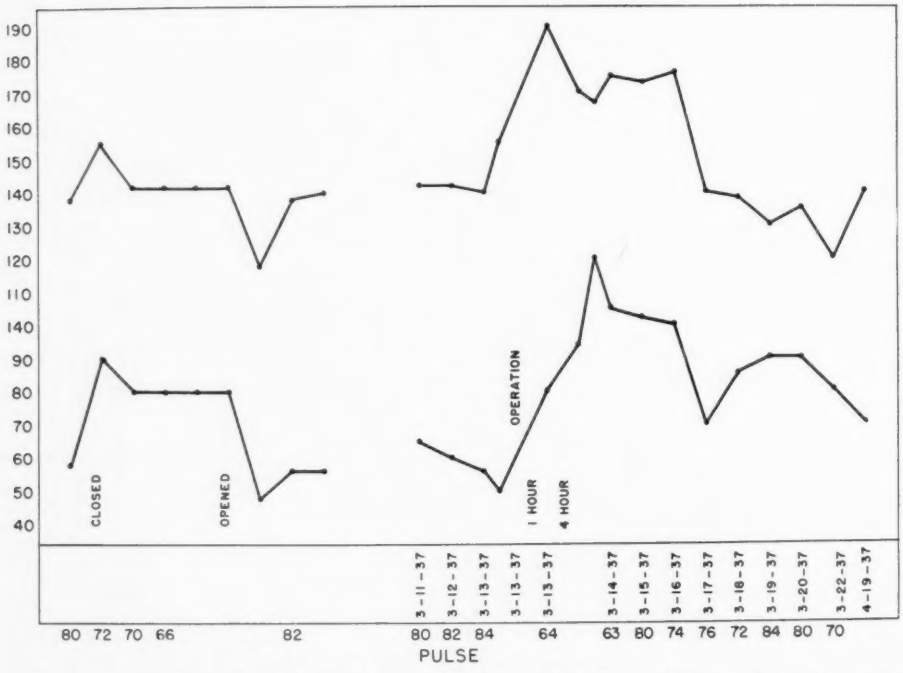


Fig. 15.—Variations in blood pressure incident to closure of a superficial femoral fistula of five years' duration. (a) By digital pressure; (b) by operation. The blood volume decreased from 5,040 to 4,200 c.c. following elimination of the fistula.

On Vena Caval Pressures.—On April 14, 1939, the animal in which bilateral femoral fistulas had been established three and one-half years previously was again subjected to nembutal anesthesia and under aseptic precautions the following procedures were carried out: Through an incision in the flank the right kidney was mobilized, the renal artery was ligated, and a glass cannula connected with an upright glass tubing of equal caliber was inserted into the vena cava through the renal vein. The pressure, oscillating with respiration, was recorded in centimeters of water under the following conditions:

	VENA CAVAL PRESSURE IN CM. OF WATER		
Both fistulas open	12-13	17-18	19-20
Right fistula closed			16.5-17.0
Left fistula closed	10-11	15-16	
Both fistulas closed	8.5-9	12-13	15-15.5
Both fistulas open	12.5-13	15.5-16.5	18.5-19

It was apparent that the vena cava was able to accommodate much of the increased volume of blood transmitted through the fistula under arterial pressure by an increased velocity of flow. However, it was also apparent that the vena caval pressure varied directly with the volume of blood diverted through the fistulas, being greatest with both fistulas open, least with both fistulas closed; intermediate rises in vena caval pressure occurred as one or the other fistula was opened separately.

On March 19, 1940, a second dog (Animal 3), in which bilateral femoral fistulas had been established on June 30, 1938, was investigated as to vena caval pressures. Under morphine and ether, a long glass cannula was introduced through a rent in the left external jugular vein down into the thoracic vena cava. This experiment differed from the preceding experiment in that both the abdomen and the thorax were intact. The following observations were noted, the vena caval pressures oscillating 5 to 10 mm. with respiration:

	VENA CAVAL PRESSURE IN CM. OF WATER	PULSE
Both fistulas open	9.5-10	108
Right fistula closed	6.5-7	90
Left fistula closed	7.5-8	96
Both fistulas closed	5.5-6	88
Left fistula reopened	7.5-8	
Both fistulas open	9.5-10.5	

Again, it was demonstrated that vena caval pressure was increased in the presence of bilateral femoral fistulas, the greatest increase occurring when both fistulas were open. Closing one or the other fistula lowered the venous pressure 2 to 3 cm.; whereas, closure of both fistulas simultaneously lowered it 4 cm.

On March 4, 1940, the dog in which two femoral fistulas had been established on Oct. 31, 1934, was again anesthetized; the remaining left renal vein was cannulized for vena caval pressures, and the remaining left carotid artery was cannulized for arterial pressures (Fig. 16). It is evident from the kymographic record that, when both fistulas were open, the vena caval pressure was high and carotid pressure was low; when both fistulas were closed, vena caval pressure was low and carotid pressure was high. Intermediate arterial and vena caval pressures were obtained, depending on closure of one or the other fistula.

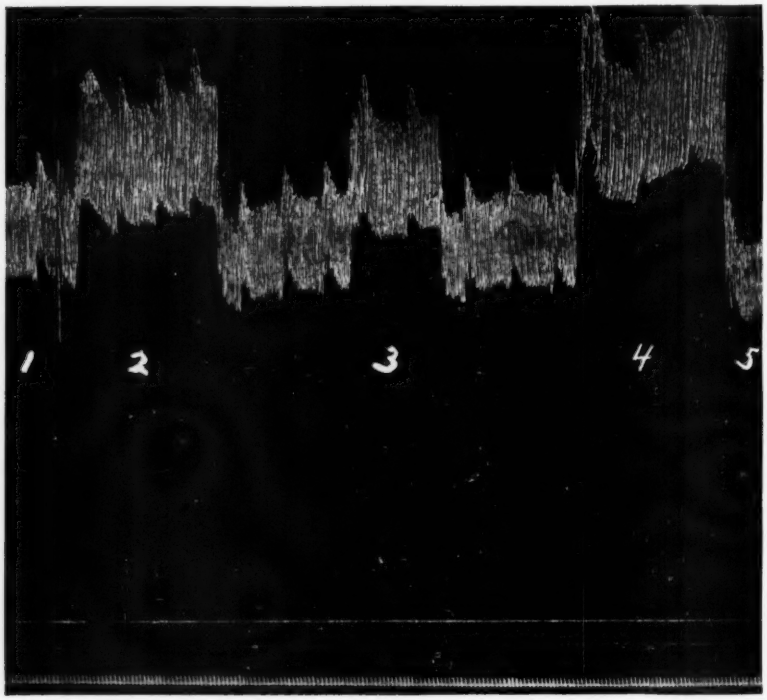
From these many observations one may conclude (1) that a rise in venous pressure occurs proximal to an arteriovenous fistula, and (2) that the extent of this rise in venous pressure depends upon the amount of blood diverted into the shorter circuit, which is determined by the size of the fistula.

SUMMARY

In the first twenty-four to forty-eight hours after the establishment of a large arteriovenous fistula, the heart diminishes in size, followed, if the animal survives, by a prompt return to normal, and, subsequently, by a gradual dilatation which may be apparent within four to five days.

Death due to an excessive diversion of blood through the fistula may occur, accompanied by a marked diminution in cardiac size.

A marked diminution in cardiac size accompanies shock.



Conditions at Site of Fistulae	Mean Arterial Pressures Carotid Artery mm. Hg.	Vena Caval Pressures cm H_2O
1. Both Open	136	13 – 15
2. Left Closed	160	9 –10.5
3. Right Closed	156	8.5–10
4. Both Closed	182	6 – 7
5. Both Open	120	13 – 14

Fig. 16.—Kymographic record of carotid arterial pressures dependent upon conditions at site of bilateral femoral fistulas of five and one-half years' duration. Vena caval pressures obtained by cannulization of renal vein.

A marked decrease in cardiac size also accompanies hemorrhage, the diminution in the size of the heart being commensurate with the degree of blood loss.

The size of the heart conforms accurately to the volume of blood flowing through it.

The dilatation that accompanies an arteriovenous fistula is not restricted to the heart, but affects the vessels involved in the fistulous circuit. The same cause is responsible for both dilatations; namely, an increase in the volume or bulk of blood flowing through that part of the circulatory system through which the blood short circuited by the fistula must flow; i.e., all the chambers of the heart, the proximal artery, fistula, and the proximal vein.

In the growing animal the dilatation may be very great without evidence of decompensation and may be accompanied by pronounced hypertrophy. It is suggested that, when dilatation outstrips hypertrophy, decompensation occurs; when dilatation is paralleled by an equivalent hypertrophy, great enlargement and dilatation of the heart may occur without decompensation.

In a crucial experiment involving three litter mates of equal weight and stature, one acting as control, one having an aorta-vena cava fistula 12 mm. in circumference, and one having an aorta-vena cava fistula 18 mm. in circumference, there occurred an increase in blood volume commensurate with the size of the fistula.

In the same animals an increase in the capacity of the circulatory system occurred, also commensurate with the size of the fistula. The increase in capacity and the increase in blood volume closely paralleled each other.

In an animal with bilateral femoral fistulas the increase in blood pressure and reduction in pulse rate were greatest when both fistulas were closed simultaneously, and considerably less when either fistula was closed separately. The physiologic effect of a fistula, therefore, clearly depends upon the volume of blood diverted through the fistula, which is determined by its size.

The transient high systolic and diastolic pressures that persist for several days following operative closure of a fistula are due to the increase in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance.

In animals having bilateral femoral fistulas, vena caval pressures were highest with both fistulas open, least with both fistulas closed, and intermediate pressures were obtained on closing one or the other fistula separately. Venous pressures proximal to a fistula are determined by the volume of blood diverted through the fistula and therefore by the size of the fistula.

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PROGRESSIVE LYMPHEDEMA ASSOCIATED WITH RECURRENT ERYSIPELOID INFECTIONS

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DISCUSSING elephantiasis, Matas[1, 2] first in 1911 and later in 1913 described the similarity of the clinical picture of recurrent erysipelas and that of the acute attacks of recurrent lymphangitis occurring periodically in cases of progressive lymphedema which terminate in elephantiasis. Since these publications, many clinical and experimental reports concerning the etiology and pathogenesis of this disease have been made. Much of the evidence tends to support secondary infection, principally that of streptococcus, as a major etiological factor. However, these investigations do not establish a definite etiology and, as a result, the present methods of treatment remain empirical and have not proved entirely satisfactory.

ETIOLOGY

Reporting the demonstration of the ova and worms of *Filaria bancrofti* in the lymphatics and lymph glands of patients with tropical elephantiasis Manson[3] in 1898 re-emphasized in the production of this disease the importance of an inflammatory obstruction of the lymphatic system resulting from infection by filaria. As a result of this report, elephantiasis was for a long time considered a disease of the tropics resulting from an infestation of the lymphatics and lymph glands with filaria. However, it was not long before there appeared reports of cases of elephantiasis in patients who had at no time been in the tropics. The progressive development of lymphedema, with associated attacks of acute lymphangitis, as well as the end stage of the elephantoid condition were essentially the same in both the tropical and nontropical varieties of this disease. The reports of these sporadic cases immediately opened to question the role of filaria as the only etiological agent in this disease. Cases occurring in the tropics in patients who give no history of filariasis and in whom the filaria organism cannot be demonstrated make exceedingly doubtful the specificity of filaria as an etiological agent even in tropical cases.

In discussing the etiology of this disease, one must constantly bear in mind the similarity of the attacks of acute lymphangitis to those of recurrent erysipelas. Because of this similarity, the possibility of a common etiologic factor's being responsible for both erysipelas and the acute exacerbations in elephantiasis must be considered. In 1883 Fehleissen[4] reported the successful isolation and culturing of streptococci in skin lesions in cases of erysipelas. In addition to the isolation

of the organism, he reproduced erysipelas with pure cultures of streptococcus in seven persons suffering from malignant growths. He also fulfilled the principles laid down by Koch which are necessary to demonstrate the specificity of an organism in a disease by reproducing the disease in animals and successfully recovering the organisms from them. Shortly after this report of Fehleissen,[4] numerous other workers reported cases of erysipelas from which they isolated various other organisms; i.e., staphylococci and pneumococci. In some instances these other workers offered experimental reproduction of erysipelas in animals as evidence that their organisms were capable of producing erysipelas. However, these investigations were never conclusive and have never seriously challenged the role of the streptococcus as the etiologic agent in cases of erysipelas. At present it is conceded that erysipelas is the direct result of an infection by streptococci.

In more recent years attention has been focused on the study of the specificity of strains of streptococci recovered from cases of erysipelas as compared to the strains recovered from other streptococcal infections, principally that of scarlet fever. By means of agglutination, agglutinin absorption, and in vivo experiments with homologous and other strains of streptococci isolated from cases of erysipelas and with streptococci recovered from cases of scarlet fever, Birkhaug[5-8] and Eagles[9, 10] demonstrated definite evidence of specificity of strains recovered from cases of erysipelas. Similar experiments by Gay and Morrison[11] did not confirm this specificity. Because of this conflicting evidence, an attempt was made to demonstrate the specificity of these strains of streptococci by studying toxin and antitoxin reactions of the various strains. Subsequent in vitro and in vivo neutralization experiments with toxin and antitoxin by Birkhaug,[5-8] Dick and Dick,[12] Andrewes,[13] and Stevens and Dochez[14] suggest the possibility of the specificity of the strains of streptococci recovered from cases of erysipelas. On the other hand, Singer and Kaplan[15] were unable to confirm the results of Birkhaug[5-8] and others with neutralization experiments and concluded that the streptococci of scarlet fever and erysipelas were not biologically specific. Because of the lack of uniformity of the results of these experiments, at the present one must conclude that erysipelas is caused by hemolytic streptococci which may or may not be specific for this disease.

Stevens and Dochez,[14] Stevens,[16] and Francis,[17] by means of skin tests performed both during the acute phase of and in the convalescence from the disease, were able to demonstrate a local tissue sensitivity to metabolic products from cultures of streptococci recovered from cases of erysipelas. Stevens[16] compared these focal reactions to reactions seen in tuberculous patients following the injection of tuberculin. Amoss[18] observed similar reactions in a child with staphylococcus infection resulting from the injection of a staphylococcus filtrate of the organism recovered from the patient. Stevens[16] produced focal responses with homologous streptococcal filtrates in patients suffering from strepto-

coccal infections. These observations plus the disappearance of reactions following desensitization of the involved tissue by means of the injection of increasing doses of toxin indicate a local tissue sensitivity. In other words, following an initial streptococcal infection, the tissues may become sensitive to the toxins and metabolic products of these organisms and therefore will react in a similar manner to these toxins and metabolites as in the original infection. These observations offer a possible explanation for the recurrent attacks of erysipelas resulting from foci of infection in more distant tissues.

Hutchinson[19] in 1904 stated that whatever causes an obstructive inflammation of the lymphatic trunks may in dependent parts produce elephantoid hypertrophy. This statement aptly describes the pathogenesis of the disease under discussion, but it does not establish definite etiology of the obstructive inflammation. Sabouraud[20] in 1892, followed by Moncorvo[21] and Unna[22] in 1896, reported the demonstration of streptococcus in patients with recurrent erysipelas and elephantiasis. They believed that the recurrent inflammation of the lymphatics resulting from an infection by the streptococcus was responsible for the production of nontropical elephantiasis. Unna[22] emphasized the importance of the inflammatory exudate in addition to simple obstruction in producing fibromatosis characteristic of elephantiasis. He explains the periodic occurrence on the basis of incomplete healing of the original lesion resulting in a vascular disturbance and the incomplete destruction of the streptococci. As suggested by Matas,[1, 2] there are probably many cases of tropical elephantiasis in which the filaria plays no part but which are the result of repeated infections of the lymphatic system by pyogenic organisms.

The above opinions are corroborated by the observations made in the tropics by several workers who reported numerous cases of elephantiasis in which there was no history of filaria and in which filarial organisms could not be demonstrated. In 1921 Rose,[23] by an analysis of previous reports of Grieve[24] (1883), Conyers and Daniels[25] (1886), Daniels and Castellani[26] (1908), and of his own statistics (1920), showed the incidence of elephantiasis in British Guiana to vary between 3.9 and 19.2 per cent; whereas, the incidence of clinical filariasis was between 14.8 and 25.3 per cent. He further showed that secondary infection by bacteria plays an important part in the production of elephantiasis in the tropics, stating that one can recover a pure culture of streptococcus in 90 per cent of the cases of elephantiasis from the "juice" or pus from the acutely inflamed regional lymph glands. In other cases he found a mixture of organisms, including streptococcus, *Staphylococcus albus*, *Bacillus coli*, and *B. pyocyaneus*. In 1908 Powell[27] was unable to demonstrate filaria in any of seven cases afflicted with elephantiasis in Bombay. He found 5 per cent of a large number of inhabitants examined for filariasis to be infected with the organism, yet free from elephantiasis. Megaw[28] in 1908 reported that

of 100 prisoners examined only 3 had elephantiasis; whereas 15 of the entire number were found to be infected with filaria. The three patients with elephantiasis gave no history of filarial infestation and the larvae could not be demonstrated in their blood on repeated examinations. Dubruel[29] in 1910 concluded that the tropical form of elephantiasis is more closely allied to the sporadic form and should be considered contagious during the attacks of erysipelas. His conclusions are based on the examinations of the inhabitants of the island of Morrea where about 12 per cent of the population have elephantiasis, yet he was able to demonstrate filaria in only 1 case; whereas, in many he found streptococcus in pure culture. He failed to state the areas from which these cultures were obtained. In 1930 Suarez[30] reported the study of 60 cases of recurrent lymphangitis associated with elephantiasis of the lower extremities. Cultures obtained from subcutaneous tissues in 50 patients were negative in all but 2 cases in which streptococci were found. In the remaining 10 cases cultures were made from septic foci; the hemolytic streptococcus was cultured in 9 and the hemolytic *Staph. aureus* in 1. Repeated examinations for microfilaria in the blood were negative in all of these cases. Croll stated that 11.5 per cent of 4,000 Europeans admitted to Brisbane Hospital in Australia showed filarial infection, but none had the symptoms of elephantiasis. McKinley,[31] in attempting to repeat Suarez' work,[30] obtained cultures by aspiration of the subcutaneous tissues in 27 patients, in none of whom was there any growth. Of 9 additional cases in which cultures were taken from ulcers or other septic foci, hemolytic streptococci were found in 7 instances and hemolytic *Staph. aureus* in 2. In 11 other patients he obtained cultures from sections of the skin and found the green streptococcus in 1 and the hemolytic *Staph. aureus* in another. The inconsistency of these findings led him to believe that bacterial infection does not always or even commonly play a role in acute filarial lymphangitis and that it is possible to have acute lymphangitis of filarial origin without bacterial invasion. In 1932 Acton and Rao[32] suggested the following two possibilities by which filaria can produce lymphatic obstruction: (1) by chronic inflammation and obstruction resulting from repeated and prolonged damage to the lymph glands by the passage of the larvae through them; (2) by an acute inflammatory change in and around the glands which have been damaged previously by the larvae, this inflammation usually being caused by pyogenic cocci. These hypotheses of Acton[32] are unusually interesting in that they offer a possible explanation why elephantiasis is more prevalent in the tropic than in the temperate zone. Matas[1, 2] suggests that the mode of living of natives in the tropic zones continually exposes the skin to both minor and major injuries which serve as a portal of entry for pyogenic organisms. Both Matas and Acton maintain a neutral attitude in not trying to attribute all cases of elephantiasis to infections by either filaria or pyogenic organisms. This is particularly significant in that, in spite of the

progressively accumulating mass of evidence in favor of an etiologic pyogenic infection, there are undoubtedly cases of elephantiasis which can be explained solely as a result of filarial infection. However, the evidence indicates that even in tropical elephantiasis the role of secondary infection is assuming major proportions.

As mentioned previously, Sabouraud[20] and Unna[22] were the first to call attention to the possible etiologic significance of streptococci in cases of progressive lymphedema associated with erysipelas-like attacks. It is upon such evidence that the etiology in the nontropical variety of elephantiasis can be established. In 1921 Halsted,[33] in discussing lymphedema following radical mastectomy, demonstrated that radical excision of the axillary glands or axillary vein or both will not in themselves produce this condition. There must be, in addition to the interference with lymphatic and blood flow, a secondary infection in order to produce elephantiasis of the upper extremity. Sistrunk[34] in 1921 reported 33 cases of elephantiasis, 9 of which were proved definitely to be the result of some infection in various types of wounds. He failed to mention whether or not cultures were obtained. Reichert[35] in 1929 made the following statement: "Simple lymphedemas are the result of stasis. Add the factor of infection, and we have an entirely different picture, that of elephantiasis. Chronic infection, usually caused by streptococcus, after a time readily leads to a progressive hypertrophy of the hypodermal and dermal connective tissues. Simple mechanical blockage of the lymphatics causes regional lymphedema but the characteristic fibromatosis and histological changes peculiar to the elephantoid states cannot be produced without pyogenic infection." Kuntzen[36] in 1930 stated that lymphatic obstruction plays the major role, erysipeloid streptococcal infection being secondary in the production of elephantiasis and pyogenic infection acting only to intensify the course of the disease. Castellani[37, 38] in 1934, in addition to *Staph. aureus* and *Staph. albus*, *Staph. viscidus*, and hemolytic and nonhemolytic streptococcus, found two rare coccobacilli, *Micrococcus meta-myceticus* and *M. micromyceticus*, in cases of nonfilarial elephantiasis. More recently, Tisseuil,[39] Gougerot and Vial,[40] and Telford and Simmons[41] report other cases of elephantiasis which probably resulted from pyogenic infection.

Supporting the clinical evidence that streptococcus plays a major etiologic role in the production of elephantiasis is the work of Homans,[42] Drinker, and their co-workers.[43-46] They were able to reproduce typical lymphedema in dogs by injecting a mixture of quinine and silica into the lymphatics. One of these dogs developed spontaneously an acute illness which in many respects resembled cases of recurrent erysipelas or exacerbations of lymphangitis. From material aspirated from the edematous limb during the acute attacks, cultures of streptococci were obtained which, when injected into a normal dog, failed to produce a lesion but which, when injected into an edematous limb, reproduced a similar attack. These workers suggest that, even though streptococci

may not be responsible for the initial lymphatic obstruction producing lymph stasis, lymph stasis predisposes the involved area to pyogenic infection. Prior to the work of Drinker,[43-46] Homans,[47] and others, Reichert,[35] Homans,[47] and Homans and Zollinger[48] had attempted to reproduce lymph stasis in dogs by the simple blockage of lymphatics, by employing various techniques. In additional experiments Homans also ligated the femoral vein. By these methods they were able to produce only a transient lymphedema of approximately two to three weeks' duration and concluded that the failure to produce permanent edema probably was due to the rapid re-establishment of the severed lymph channels.

Various authors have suggested other etiologic agents as responsible for this disease. The demonstration of Sulzberger and co-workers[49] of a sensitivity to the trichophyton in the involved area is indicative that this fungus may be of etiologic significance in some of the cases. They offer as additional evidence the improvement resulting from desensitization to the trichophyton. Mulholland[50] states that many of the cases seen on the third surgical division of Bellevue Hospital of New York show a marked improvement with decrease in swelling once the epidermophytosis has been eradicated. Other authors, observing a similar relationship between epidermophytosis and elephantiasis, believe that elephantiasis is not a result of the epidermatophytosis but of infection by the streptococcus which in many instances can be isolated from cracks and fissures of the skin associated with the fungus infection.

In 1933 Stevens,[16] in discussing chronic infectional edema, advanced the theory of local tissue sensitivity to the metabolic products of the streptococcus. From cultures which he obtained by aspirating the lesions, filtrates which he used for immunization were made. He would invariably reach a critical dose which would cause a reaction at the site of injection similar to that seen in exacerbations. Continued immunization caused a development of immunity to the toxin in much larger doses. The following quotation from Stevens[16] is evidence to support this idea: "While impaired venous and lymphatic circulation is seen to be important in the pathogenesis, in the arm and leg, edema of the face has followed infections without similar predisposing circulatory disease—chronic infections of the sinuses have, however, appeared important in this respect. Four of five patients with facial edema had infected antra or ethmoidal sinuses. The importance of these infections is emphasized by the absence of similar infections among the fourteen patients in whom edema has not developed." In 1928 Francis[17] reported results of skin tests done on 30 patients with sterile filtrates prepared from a culture of hemolytic streptococci obtained from a typical case of erysipelas; 20 cases during the active stage of the disease showed either no or only very slight reaction; whereas, 10 cases showed a definite response. Test doses repeated as the disease progressed toward convalescence showed a general tendency for sensitivity of the skin to increase instead of de-

crease and ultimately become negative. These tests were performed in cases of acute erysipelas and are mentioned only to illustrate and support the hypothesis of tissue sensitivity to streptococcal filtrates.

Numerous authors have reported various conditions which produce lymphedema which in some instances progress to the elephantoid state. As this paper is concerned only with the type resulting from periodic recurrent attacks of lymphangitis (erysipeloid), no other will be considered. The summary of the various factors which have been suggested as causing these attacks which result in the typical elephantoid limb may be classified as follows: (1) filarial; (2) filarial plus pyogenic infection; (3) lymphatic obstruction other than filarial plus pyogenic infection; (4) pyogenic infection (streptococcal); (5) local tissue sensitivity: (a) metabolic products of streptococci; (b) trichophyton.

PATHOGENESIS

In order to understand more clearly the pathogenesis of this disease, it is important to review the anatomy and the physiologic functions of the lymphatic system. In general the lymphatic system consists of anastomosing networks of capillaries which in turn drain into larger lymphatic trunks, which are interrupted in various places by interposed lymph glands. These glands have both afferent and efferent vessels, the latter emptying the lymph into larger ducts and eventually into the thoracic ducts which terminate in the subclavian veins. The lymph capillaries consist of a closed system of vessels composed of a single layer of flat endothelial cells which are bathed in tissue fluid. Lymph capillaries are found in every organ possessing a blood vascular circulation. However, we are concerned only with the lymphatics of the connective tissues of the extremities; therefore a discussion of the lymphatics of the other organs will not be included. In the skin the capillaries are found in the dermis. According to Gray,[51] the subcutaneous tissues are without capillaries but contain small lymphatic vessels. The capillary system of the muscles is not clearly understood, but it is generally conceded that muscle contains fewer plexuses of lymphatic capillaries than do the more superficial tissues. The osseous system, including the periosteum and bone proper, contain abundant capillaries. In the extremities the capillary systems are divided into two parts between which there is very poor, if any, connection. The superficial lymphatic system of the upper extremity, however, has many more communications with the deeper system than are found in the lower extremity. The superficial capillary system of the upper extremity empties into lymphatic vessels which follow the course of the superficial vascular tree and terminate in the epitrochlear and axillary lymph glands. The deep lymphatic system consists of capillaries which drain muscle tissues, intermuscular connective tissues, and the osseous system; these coalesce to form four sets of lymphatic trunks: (a) radial, (b) ulnar, (c) volar, and (d) dorsal. These four trunks follow the respective vessels of the deep circulation and terminate in the axillary glands.

In the lower extremity the superficial lymphatics consist of anastomosing plexuses of capillaries in the dermis which coalesce to form lymphatic trunks in subcutaneous tissues. There are two sets of these lymphatic trunks; the median which follows the course of the great saphenous vein terminating in the femoral or subinguinal lymph nodes, and the lateral trunks which follow the lesser saphenous vessel to the popliteal lymph glands. It is in this region that there is a possible communication between the superficial and deep systems of lymphatics. As in the upper extremities, the deeper plexus drains similar tissues and its trunks follow the deeper vessels of the vascular system, terminating in the external iliac lymph nodes. Efferent vessels from the femoral and inguinal glands also drain into this group of nodes. The efferent vessels from the iliac nodes then communicate with the hypogastric and lumbar glands, finally terminating in the thoracic ducts, which empty into the subclavian veins.

The propelling forces producing lymph flow depend for the most part on two functions: the presence of arteriolar pulsations, as shown by McMaster and Parsons[52] and by Cressman and Blalock;[53] and the active and passive contraction of skeletal muscles. In order to insure centripetal flow, the large lymphatic vessels contain valves which are attached to the vessel wall by the convex edges, the concave edges being free and in the direction of the current. These valves are lined by a single layer of endothelial cells. In most instances two valves of equal size are opposed to each other and they become more numerous as the lymphatic vessels approach the lymphatic glands. Factors increasing the flow of lymph besides the contraction of skeletal muscles and arteriolar pulsations include increased functional activity of the part by increased venous pressure or by general local hyperthermia. Allen[54] states that the rate of flow is modified but little, if any, by peripheral section of nerves or increased arterial pressure. Intravenous injections may cause increased flow of lymph by effecting the greater movement of fluid out of blood vessels or by injury to the capillary endothelium allowing proteinized fluid from the blood vessels to leak into the tissues. Any other factors causing increased capillary permeability, such as inflammation, may also accelerate the flow of lymph. Another factor increasing capillary permeability is a relative anoxia of the endothelium produced by decreased circulation resulting from arteriolar spasm.

The composition of lymph is similar to that of plasma in that it contains the same constituents of plasma but in a more diluted form. The specific gravity of lymph is approximately 1.015. According to Lowenberg,[55] the protein content of tissue fluid under normal conditions is approximately 1 per cent. Allen[54] in an analysis of dog's lymph found the protein content to be between 0.5 and 1.84 per cent. In addition to protein lymph contains nonprotein nitrogen, urea, creatinine, sugar, chlorides, fibrinogen, prothrombin, leucocytes, amino acids, phosphorus, and calcium. The cellular constituents of lymph under nor-

mal conditions consist of about 95 per cent lymphocytes. Under conditions producing inflammatory reactions, the total cell count may increase, the additional cells consisting mainly of polymorphonuclear leucocytes.

Numerous workers have demonstrated that lymph stasis alone is not sufficient to produce the elephantoid condition. Unna[22] and Sabouraud[20] contended that there must be a superimposed inflammatory reaction which keeps the cells bathed in the products of bacterial and cellular disintegration. If such is true, it is easy to understand why such conditions as congenital deformities or developmental abnormalities in lymphatic channels or tumors interfering with lymphatic flow or any other similar condition which interrupts the lymphatic passages may produce lymphedema without causing the changes characteristically found in the typical case of elephantiasis. Experiments to produce lymphedema, such as those of Homans[47] and Reichert,[35] which in brief consisted mainly of mechanically interrupting lymphatic trunks, blood vessels, or both, proved ineffectual in producing a permanent lymphedema, much less an elephantoid condition. Drinker and his associates[42-46] were able to produce permanent lymphedema in dogs by the repeated injections of an irritating substance into the lymphatics. One or two of these dogs spontaneously developed an attack simulating the attacks observed in human beings. During this seizure they were able to isolate a streptococcus. Following the initial attack, spontaneous recurrences occurred periodically with a gradual increase in the size of the limb, more closely approaching that of elephantiasis. Clinically Halsted's[33] cases are similar examples in human beings.

The pathologic picture in a fully developed case of elephantiasis with its marked fibrous tissue proliferation is probably largely the result of increased protein content of interstitial fluids. This development of the elephantatic limb is gradual, occurring over a period of years. A cross section of a limb in a fully developed case shows a marked thickening of the derma and subcutaneous tissues. This thickening consists of an increase and hypertrophy of the fibrous tissue which extends to and occasionally involves the deep fascia. The underlying muscles usually show no changes, but occasionally they may be atrophic. Scattered throughout the fibrous connective tissues are dilated lymphatics which weep on cutting them. The blood vessel walls may show some thickening, but these changes are not as marked as are the other changes.

Irrespective of the inciting nature producing the initial lymph stasis, it is probably the inflammatory reaction with its exudative characteristics which causes the excess accumulation of proteins in the tissue fluid. A vicious circle is set up in that, in addition to the increased production of protein in the interstitial fluid from the inflammatory reaction, there is interference with the normal flow of lymph predisposing to excessive protein accumulation and fibrosis.

Numerous workers, such as Allen and co-workers[56, 57] Drinker,[42-46] and others,[58-60] have shown that in experimental and clinical lymphedema tissue fluids contain between 2.7 and 4.5 per cent protein. Drinker and his associates,[42-46] experimenting with dogs, determined the protein content of plasma, lymph, and fistula fluid in a dog with elephantiasis. These were found to be 7.8, 5.5, and 4 Gm. per 100 c.c., respectively. This accumulation of protein favors the production of fibrous tissue, which results in fibromatosis in cases of elephantiasis. That such a mechanism undoubtedly operates in cases of lymph stasis with associated recurrent attacks of inflammation is suggested by this experimental work.

One should not dissociate the clinical features of the elephantoid condition from the progressive pathologic changes resulting from preceding acute attacks of lymphangitis and upon which the manifestations of the late stages depend. Matas[1, 2] in 1911 and 1913 suggested that there are probably many factors capable of producing initial lymph stasis of both the inflammatory and noninflammatory types and that resulting edema, regardless of its mode of onset, increases the susceptibility of the involved area to infection by pyogenic organisms. He further states that once the inflammatory process has occurred the clinical picture and pathologic changes are identical, regardless of the initiating etiology. The acute inflammatory reaction is characterized by painful swelling of the infected area. This area becomes red and in many respects resembles the discoloration seen in erysipelas. However, the redness is more diffuse and seldom shows the blanching in the receding area behind the advancing red margin, as is characteristic in erysipelas. The regional lymph glands of the involved area become very much enlarged and tender. Numerous men report that in the extremities the acute reaction is seldom seen beyond the root of the limb. As this disease is primarily one of lymphangitis and not one of cellulitis, this observation can be explained on the anatomical arrangement of the lymphatics. Further extension of the process can only occur in the direction of the lymphatics, this being to the internal group of lymph nodes in the pelvis and aortic areas. However, it is conceivable that in rare cases the extension onto the lower abdomen from the thigh is possible by means of a retrograde flow of lymph. The tense lymphedema accompanying each attack of lymphangitis recedes somewhat as the disease subsides, but the size of the extremity never returns to that prior to the onset of the attacks. Consequently, the affected area becomes progressively larger with each attack and there is a permanent residual thickening of the subcutaneous tissues. This process is persistently progressive, eventually resulting in typical elephantiasis.

Histologic description, as given by various authors, has some minor differences as to the changes observed in cases of elephantiasis. Early descriptions, particularly those of Unna, emphasized changes in the venous system which consist of markedly dilated veins, possessing thick-

ened walls. Recently, attention has been focused on the alterations in the lymphatic system. Descriptions of these changes differ, some authors describing marked dilatation of lymph capillaries and smaller lymph vessels, others describing lymph soaked tissues in which they can find no evidence of existing lymphatic channels. Almost all authors agree that there are distinct areas showing coagulation of lymph within the lymph vessels. The changes occurring in the skin consist of a thinning of the epidermis with a thickening of the dermis. Occasionally a thickened epidermis showing hyperkeratosis has been described. The hair follicles disappear and the sweat glands show some degree of hypertrophy; collagen fibers of the subcutaneous tissues are swollen and are arranged in parallel bundles. The bundles, and in places the individual fibers, are widely separated by edema fluid. The overproduction of fibrous tissue replaces much of the adipose tissue and connects the skin with the thickened deep fascia. Elastic fibers, if present, are arranged in frayed bundles in which the individual fibers may be broken. Most authors state that there is a disappearance of elastic fibers. There is some disagreement as to changes observed in the blood vessels, but a thickening of the vascular wall is mentioned by many. The perivascular tissues show a slight round-cell infiltration.

CLINICAL MANIFESTATIONS

The prominent features of this disease during acute exacerbations in many respects resemble those of erysipelas. The attacks are usually ushered in by a feeling of dull pain which rapidly becomes acute in the affected areas. The pain is followed by marked pyrexia, at times associated with chills, and a sustained fever. Other constitutional symptoms are those of headache, anorexia, vomiting, and occasionally a depression of the central nervous system which may produce coma. In addition to the local pain there is a marked swelling of the limb with diffuse redness and pain in the regional lymph glands. The swelling, which is tender, is rather tense and does not pit. The duration of these attacks varies from two to eight days, occasionally lasting longer. Recovery, in contrast to the onset, is gradual; the temperature falls by lysis and the other manifestations become less prominent over a period of time. The above attacks have an acute onset and an irregular periodicity which is very characteristic. The onset occurs without warning and within a few hours the symptoms usually reach their maximum intensity. The intervals between attacks vary greatly; they may occur as frequently as once every week, but usually not more so than once a month and in many cases their recurrence may not take place more often than once in eight to twelve months. In the beginning these recurrences usually appear after longer intervals and, as the disease advances, these intervals become progressively shorter.

The clinical manifestations of elephantiasis are usually limited to the inconveniences caused by the extensive enlargement of the involved

area. In some instances this may be so extensive that complete loss of function is the result. The patient's complaints are almost entirely limited to those of inconvenience, plus a dull pain which is frequently associated with the increased weight of the involved extremity. In addition to the marked increase in size of the extremity the overlying skin is rough and coarse, having a *peau d'orange* appearance. At times the mouth of the hair follicles are gaping and the hair is usually very coarse. In the region of the ankle and knee the hypertrophied integument is thrown into heavy folds. Frequently, weeping ulcers with a surrounding eczematoid skin are present in the lower leg. In the region of chronic ulcers the skin is often pigmented and contracted, giving the appearance of an annular constriction.

Fig. 1.—X-ray of lower third of leg. *A*, Normal; *B*, elephantiasis.

In addition to the differences in the types of edema caused by other conditions due to systemic disease, including cardiorenal pathology, myxedema, etc., Reichert[61] demonstrated the differences in x-ray findings of elephantiasis from the other edemas. He illustrated that in the advanced stage of lymphedema and elephantiasis there is a coarse trabeculation as well as marked thickening of the subcutaneous tissues. The muscle tissues and other deeper structures retain their relative normal size. These points are easily made out in soft tissue x-rays and are a diagnostic aid because in similar x-rays in other conditions with edema all of the tissues are usually involved. Our x-rays illus-

trate coarse trabeculation of subcutaneous tissue as described by Reichert.[61] (Figs. 1, 2 and 3).

As suggested earlier, the successful treatment of this disease in all probability will depend upon a clear understanding of the etiologic factors and pathologic changes occurring during its course. Unfortunately, the patient seldom consults the physician during the initial attack or even early in the course of the disease. Even if the patient did consult the physician during the acute attack before the onset of characteristic fibromatosis, it is doubtful whether a diagnosis of pro-

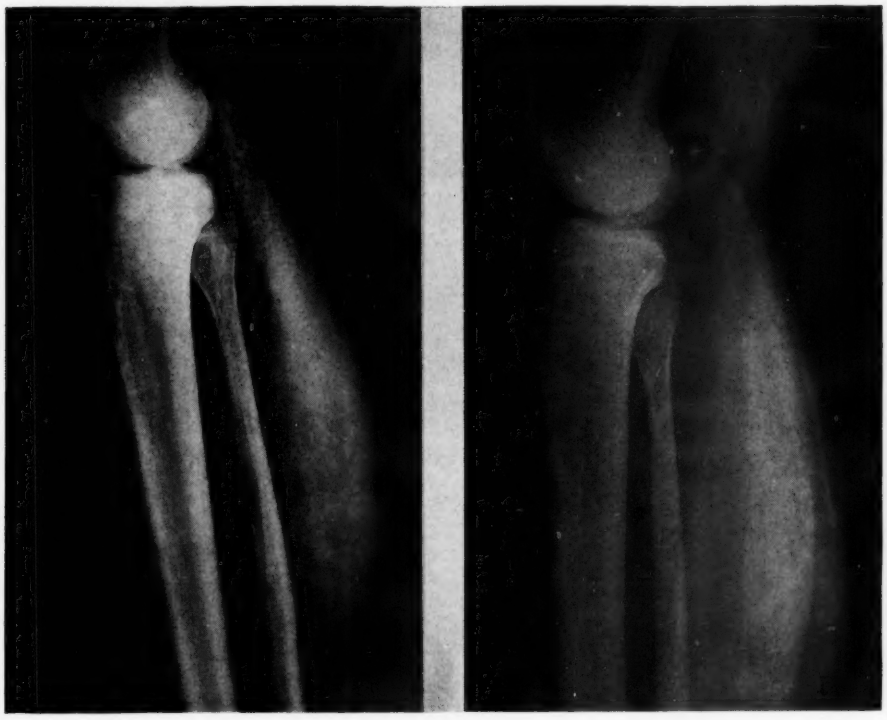

Fig. 2.—X-ray of upper third of leg. *A*, Normal; *B*, elephantiasis.

gressive lymphedema would be made; it is more likely that the patient would receive treatment for recurrent erysipelas. Prevention of recurrent attacks at this stage is the ideal form of therapy and every effort should be made to accomplish this. If this is successful, a great many surgical procedures will be obviated. Consequently, it should be constantly borne in mind that every case of lymphangitis is a potential case of progressive lymphedema and fibromatosis.

TREATMENT

As in the past, the therapy during the acute attacks of lymphangitis should be directed to the general systemic care of the patient plus the necessary measures to reduce local inflammatory reaction. Usually these will consist of bed rest, elevation of the extremity, and general

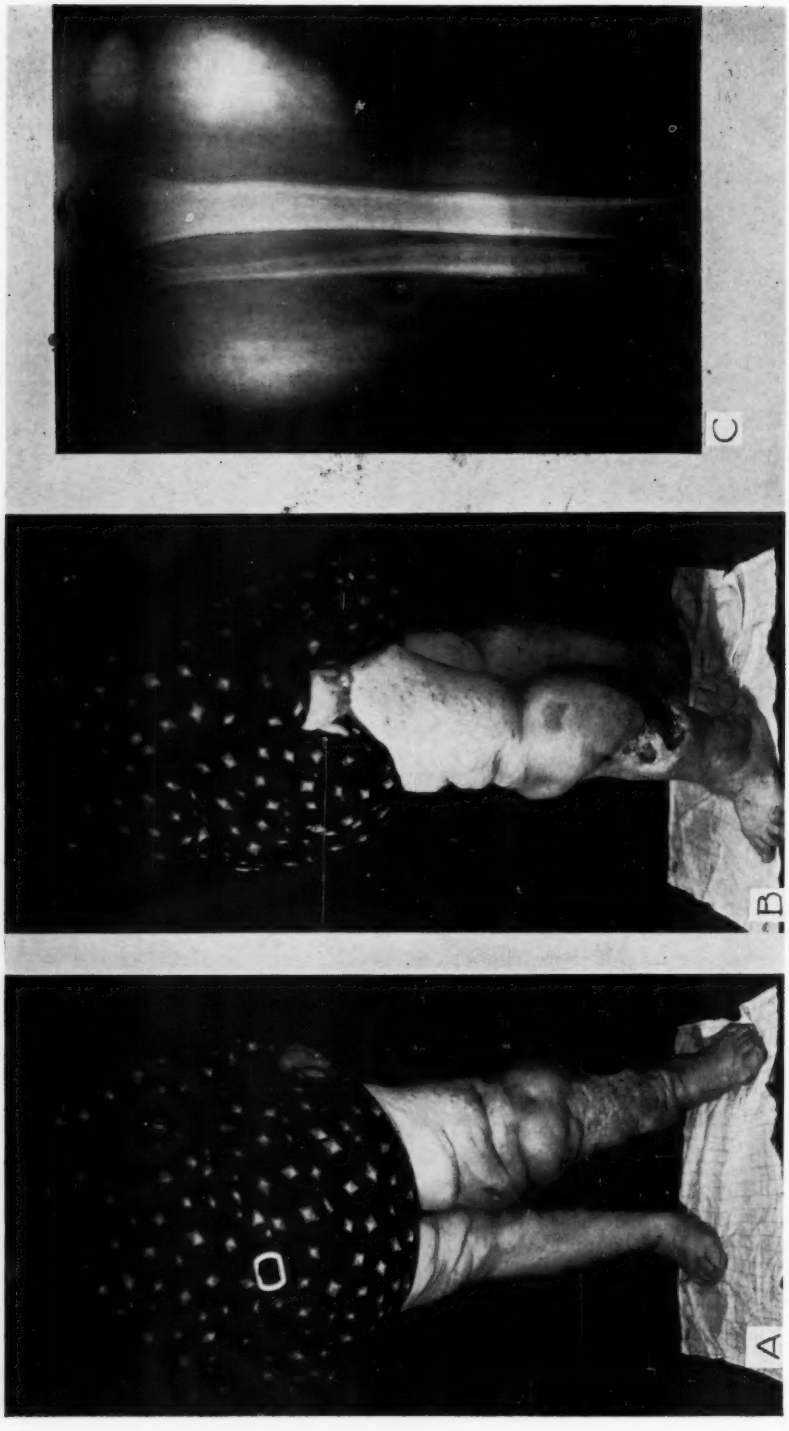

Fig. 3.—Photographs and x-ray of elephantiasis.

supportive measures. The value of vaccines and serum therapy is not questioned, but they have not proved to be of particular benefit in all cases. Beall,[62] Flexner,[63] Gougerot and Blum,[64] Muller and Jordan,[65] Benson,[66] Memmesheimer,[67] and others have tried autogenous and polyvalent vaccines with success in many instances. Vaccines have shown a tendency in certain cases to decrease the frequency of recurrences. Symmers and associates,[68-71] Dick,[12] Birkhaug,[7] Spink and Keefer,[72, 73] Francis,[17] Kolchin and co-workers,[74] and Spicer and co-workers,[75, 76] and others[77-85] found polyvalent streptococcic antiserum to be of great value in treatment of acute erysipelas, with good but not so striking results in recurrent cases. These same workers demonstrated that the use of polyvalent streptococcic antiserum does not modify in any way the frequency or the severity of recurrent attacks of erysipelas.

In addition to the specific therapy in recurrent acute lymphangitis it is important that the edema during the interval between acute attacks be prevented. The patient should keep the extremity bandaged with either an elastic stocking, rubber-roller bandage, or by some similar method; in addition baking and massage with periodic elevation of the extremity should be practiced. Exercise of the extremity when it is in the dependent position should be encouraged. These methods of controlling edema between recurrent attacks of lymphangitis could be instituted with benefit in those cases of chronic progressive edema in which there has been no history of an acute episode, because Drinker and his associates[42-46] showed that lymph stasis predisposes to secondary infection. Also, there are numerous case histories of progressive lymphedema of many years' duration in which at no time has there been a flare-up of lymphangitis or other evidence of infection, which in later stages developed the manifestations seen in the type of lymphedema under discussion. Once this vicious cycle of infection and lymph stasis has occurred, its repetition is likely, as is the resulting elephantoid condition. Consequently, every case of progressive lymphedema, inflammatory or otherwise, should be treated with this in mind and every effort made to control further progression of the edema. The importance of preventing and controlling the edema cannot be too strongly stressed. Regardless of the etiology, edema predisposes to secondary infection. The inflammatory process resulting from the secondary infection produces a transudation rich in protein into the interstitial spaces which, due to the impaired lymphatic circulation, accumulates excessively. This protein plus the other products of inflammation is ideal for the production of fibrous tissue. It is because of this susceptibility of edematous tissue that the prevention of the edema is not only prophylaxis against infection, but, if completely controlled, may arrest the condition. This prevention of edema by suitable bandaging is most important and cannot be too strongly stressed.

Matas[1, 2] first suggested that, because of the evidence favoring a streptococcal infection in this disease, an attempt should be made to immunize the patient against the streptococcus organisms. He advocated

the repeated injections of a polyvalent streptococcic antiserum over a long period of time. As evidence, he presented a patient who went through a course of repeated injections of 10 c.c. doses of antiserum, given at least three times a week. After sixteen injections the patient reported by letter from a distant city that this course of injections had given her considerable relief. However, she later reported that she had had a recurrence of lymphangitis. Matas[1, 2] advised repeating the course of injections, but does not give the follow-up of this case. Since his original report, Matas has treated several patients with elephantiasis by repeated injections of antiserum. Although this treatment has not completely arrested the disease, he feels that it is of benefit in that it lengthens the interval between the attacks of acute lymphangitis and also lessens the severity of these attacks when they do occur. Apparently, this suggestion has not received a fair clinical trial in that there are no reports of its use. At Charity Hospital and the Hutchinson Memorial Clinic in New Orleans, Matas' suggestion was attempted in eleven cases, seven of which failed to complete the full course of immunization for various reasons beyond our control. The four remaining patients have received at least one complete course of injections of antiserum and in one instance a patient has received multiple series of injections. The patient receiving the multiple series of injections of antiserum and the one other who received only one course of treatment were not benefited by this form of therapy, both having recurrences without relief. The third patient, who has almost completed his first course of injections, experienced a recurrent attack shortly after starting the injections of antiserum. However, he has been free of symptoms during the last five months and feels that inasmuch as he was having recurrent attacks of lymphangitis about once a month he has been definitely benefited. In this case the indications are not only lengthening the interval between the attacks but are decreasing the severity of their manifestations. The fourth patient did not experience a recurrence during the course of treatment and has failed to return since its completion. Bertwistle and Gregg,[84] Picard,[85] Elliott,[86] and Sézary and co-workers[87] advocate the use of antiserum in the treatment of this disease but fail to state that they have used it as outlined by Matas.[1, 2] Consequently, clinical evidence is not sufficient to warrant conclusions as to the success or failure of this method of treatment. Although the accumulating evidence of a high degree of specificity in the strains of streptococci as related to their immune responses suggests that this method of therapy at times may fail, in some specific cases it is advantageous in preventing the recurrence of acute attacks of lymphangitis. A further clinical trial is indicated but it must be constantly kept in mind that the specificity of infecting organisms in certain cases may result in failure of response.

Without explaning the rationale, Low and Dixon,[88] McGolrick,[89] and others treated elephantiasis patients with intravenous injections of

nonspecific protein using T. A. B. vaccine. They fail to mention the nature of this vaccine, but report good results in the acute phase; however, their follow-ups are insufficient to warrant conclusions. There is one report of having used sulfanilamide[90] during the acute phase, but here again there is insufficient follow-up. In our experience sulfanilamide therapy in recurrent lymphangitis has been of no particular benefit in that it did not seem to alter the course of the acute attack or prevent recurrences.

The earliest reports of cases of elephantiasis were concerned primarily with the operative therapy. Of these, the reports of Lisfranc,[91] who described a method of scarification of the tissues, and Carnochan,[92] in 1851, who reported the ligation of the external iliac or femoral artery as a method of decreasing circulation and thus decreasing edema, were the first. Carnochan's[92] procedure was used more frequently but many reported unsatisfactory results in that improvement did not follow and gangrene often developed. Handley,[93] in 1908, was the first to attempt to re-establish lymph circulation in lymphedema. His method consisted of placing silk threads parallel to the axis of the limb in the subcutaneous tissues. Various other modifications of this procedure have been advanced. Lexer[94] substituted strips of fascia for the threads, and Lanz,[95] in addition, trephined the femur and placed strips of the deep fascia into the trephined holes. Results of these procedures have been for the most part very disappointing. In 1912 Kondoleon[97] reported the procedure which bears his name. Ten Horn,[98] discussing operations used to establish increased lymph drainage, states that Payr, independent of Kondoleon, suggested a procedure similar to that described by Kondoleon. Consequently, this procedure probably should be called the Kondoleon-Payr operation. Kondoleon attempted to establish communication between the superficial and deep lymphatics by the excision of strips of deep fascia and placing subcutaneous tissues in contact with the muscle. Matas[1, 2] was the first to perform a Kondoleon procedure in this country. His comments as to the efficacy of this operation were: "It is obvious that the possibilities of the new principle can only be tested by clinical experience and further observation. All that can be said of the observations thus far reported is that they are encouraging. It is with the hope that the simple procedure of Kondoleon[97] herein described may encourage others similarly placed to give a more extended and thorough trial to the method, that these early observations are recorded." Subsequent reports[100-118] indicate the operation met with indifferent success in the majority of cases. The lack of complete success resulted in various modifications by Sistrunk,[119] Auchincloss,[120] Macey,[121] and others;[122, 123] however, all are based upon the same principle. These differ from the original Kondoleon[99] procedure in the following respects: the Sistrunk[119] modification added the removal of overlying skin and a wedge of diseased subcutaneous tissue;

Auchincloss[120] modified the Kondoleon-Sistrunk procedure by removing considerably more diseased subcutaneous tissue. In 1940, Macey[121] reports his procedure of planting a full thickness graft on the deep fascia and resuturing the elephantoid skin over the graft. Two weeks later, the subcutaneous elephantoid tissue is excised and removed from over the graft. Preceding the report of Macey,[121] Gillies and Fraser[123] outlined their plastic operation, which consists of bridging from the upper thigh to the abdomen by means of a flat pedicle graft of skin and subcutaneous tissues obtained from the arm. By this method, they attempted to establish communication between the lymphatics of the leg and those of the trunk.

Whereas blocking the sympathetic ganglia is of value in the treatment of edema associated with thrombophlebitis, both in the acute and in the chronic types, it is questionable whether it is of any value in cases of elephantiasis associated with recurrent erysipeloid infection. If, however, in a given case there is evidence of vasoconstriction either during the acute stage or subsequent to it, as can be determined by novocain block of the lumbar sympathetic ganglia, it is likely that the edema can be beneficially affected by interruption of the sympathetic impulses. Because, as previously reported by Ochsner and DeBakey,[125] vasoconstriction associated with thrombophlebitis favors the production of edema and the relief of the vasoconstriction beneficially affects the accumulation of the fluid; the production of edema in vasoconstriction is probably due to the increased permeability of the capillaries, which in turn is caused by a relative anoxia resulting from the severe arteriolar spasm. Once the fluid which is rich in protein gets out of the vascular system into the perivascular spaces, it is difficult in cases with vasospasm for it to return to the vascular system, because the pump which is responsible for the movement of lymph, namely, arteriolar pulsation, is less effective. It has been shown by McMaster and Parsons[52] and Cressman and Blalock[53] that arteriolar pulsations are largely responsible for the movement of lymph. By overcoming the vasospasm, the edema is beneficially affected, first by preventing the anoxia of the capillary endothelium and overcoming its increased permeability and preventing the excessive exudation of fluid into the perivascular spaces and also by favoring the movement of the lymphatic fluid by re-establishing the normal arteriolar pulsations. Jacquerye[126] reports nine cases of elephantiasis in which sympathectomy was done. All of these were improved with distinct diminution in the size of the extremity, disappearance of lesions and ulcers, and increase in temperature. However, the follow-up was not complete enough to warrant a final evaluation of the therapy. Basset, Haguenau, and Gauthron[127] performed a periarterial sympathectomy in a case of lymphedema without a satisfactory result. It is well known at the present time that periarterial sympathectomy is relatively ineffective in producing vasodilatation. Telford and Simmons[41] state that in the cases of chronic lymphedema in which they

have done sympathectomy the results have been disappointing, because as soon as the patient begins to walk after the sympathectomy there is an increase in the size of the extremity.

The majority of the recent operative procedures have been directed toward re-establishing a collateral lymph circulation, without taking into account the etiology of the production of the condition. In the literature there are numerous reports of workers[100-118, 128-137] using these procedures and from them it is obvious that the only value of a surgical procedure is in the removal of considerable amount of tissue, thus decreasing the size of a limb. In so doing, in many instances there has been a partial return of function in a previously useless limb. However, in almost all of the cases there has been some, if not considerable, recurrence of edema as well as recurrence of acute lymphangitis. Most authors now feel that the only indication for operation is to remove or to restore the function of a limb, which, because of its size, is virtually useless. The operation is definitely contraindicated during the early stages of the disease.

Very few authors have commented upon the reasons for failure of the various operative procedures. An obvious explanation presents itself after a careful study of the anatomy of the lymphatic system, the infectious nature of the disease, and its pathogenesis. Keeping in mind the possible etiological factors involved, it is apparent that, with the exception of those operations removing considerable tissue, none of the surgical procedures are designed to attack the etiological factors which may be present. As suggested, such operations as the Sistrunk[119] or the Auchincloss[120] modifications of the Kondoleon[97] procedure, or the recent operation of Macey[121] in removing large areas of involved pathologic tissue might possibly at the same time remove the source of reinfection. This is in agreement with Unna's[22] hypothesis that the disease is primarily one of streptococcal origin and recurrences result from persistence in the tissues of streptococcus in the dormant state during remissions. The recent work on the etiology of this disease has established the fact that in many instances the recurrences result from an entirely new exposure to the streptococcus. The portal of entry may be purely a local one, such as seen in cases resulting from local wounds, open ulcers, etc., or it may result from a more distant focus of infection, the local manifestations being explained by tissue sensitivity. A case illustrating this has been observed by one of us. This patient several years before the initial attack of erysipelas experienced a severe third degree burn of the right lower extremity which resulted in extensive cicatrization preventing the full extension of the knee. In succeeding years the patient's life was that of an active youth, participating in high school and college athletics. The activities with constant strain on the scar tissue resulted in a chronic recurring ulcer in the popliteal area. Approximately fourteen years after the injury, he experienced his first typical erysipelas attack which began above the malleolar area

and extending proximally involved the lower third of the leg. During the next four or five years, his attacks recurred at indefinite intervals, which became shortened as time progressed. During each attack the wide separation of the popliteal ulcer and the erysipelas infection was clear cut. Approximately six years after the onset and after innumerable recurrences of lymphangitis, a chronic recurrent ulcer in the popliteal area, as well as underlying scar tissue, was excised. A pedicle graft from the opposite thigh to the popliteal area was successful. Since this operation seven years ago, the patient has not experienced any further recurrences. It is obvious in this instance that stress upon the scar tissue in the popliteal area prevented the healing of the ulcer which, at a point some distance from the focus of infection, served as a portal of entry for the organisms responsible for the recurrent attacks of lymphangitis. Removal of this portal of entry resulted in a seven-year cure. Mulholland has similarly observed that in cases of recurrent lymphangitis of the erysipeloid type with epidermophytosis the dorsum of the foot is seldom involved, indicating a skip area between the toes and the erysipelous reaction. This being so, it is apparent that the operative procedure cannot offer more than temporary relief unless the source of the inciting factor is at the same time eradicated. In those cases which are a result of local infection, all local lesions should be carefully removed. In cases in which allergic phenomenon plays an important part, it is important not only to remove the foci of infection, but also to desensitize the involved area.

A review of the many etiological factors, as well as of the nature of the disease, which is primarily one of lymphangitis with secondary lymph stasis and edema, suggests that any operative procedure may be definitely harmful and is therefore contraindicated, if attempted before eradication of the inciting factors. If the source of infection persists after establishing collateral circulation of lymph, the recurrence of acute lymphangitis will only result in further extension of this inflammatory process into previously uninvolved channels. By so doing, deeper lymphatics are subjected to a pathologic process similar to that which produced the original condition. Therefore, an operation performed at this time not only opens new pathways for further extension of the disease, but at the same time by this extension of the disease tends to destroy the deep lymphatics and thus precludes the possibility of a successful operation at a later date, once the etiology has been controlled.

The importance of these foci of infection in causing the recurrence of lymphangitis in patients with progressive lymphedema cannot be overemphasized. Elliott[86] and MacKee[138] suggested that such foci could be important factors. Rhodes[139] also emphasized the importance of eradication of a focus of infection in the treatment of this disease. Stevens[16] and others, in demonstrating the acquired sensitivity of previously infected tissues, have partially explained the mechanism by

which these foci can be responsible for a recurrent lymphangitis. It is therefore obligatory for and the duty of the surgeon to search carefully for any possible focus of chronic infection in cases of progressive lymphedema. These may be found in local ulcers or fissures in associated epidermophytosis, chronic recurrent ulcers in scar tissue, and in the upper respiratory tract, including the paranasal sinuses, tonsils, teeth, and pharynx. It is important that these foci be eradicated as they may serve as ports of entry for streptococci.

SUMMARY

The role of secondary pyogenic infection, particularly that of streptococcus, in the production of recurrent attacks of acute lymphangitis resulting in elephantiasis is discussed. Elephantiasis is the end result of recurrent erysipeloid lymphangitis, produced by pyogenic infections, usually the streptococcus. Lymphedema is a predisposing factor for the pyogenic infection which causes the inflammatory reaction which is responsible for the ultimate fibromatosis.

Recurrent febrile attacks accompanying the erysipeloid lymphangitis are characteristic.

The treatment consists of prevention of the recurrent streptococcal infections and the avoidance of edema by the use of posture and compression bandages. Prolonged use of polyvalent streptococcic antiserum may be of value in some cases. Removal of foci of infection is of paramount importance.

Extirpation of diseased tissue is not justified until the infection has been eradicated. If appropriate conservative therapy is instituted early, surgical procedures usually can be avoided.

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